FISTULA CARE CONTINUUM AND INDIVIDUALIZED VASCULAR ACCESS MODELS FOR OLDER ADULTS UNDERGOING HEMODIALYSIS

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ABSTRACT

Annually over 50,000 patients who are 65 years and older initiate hemodialysis in the United Studies. Choosing a vascular access for older dialysis recipients is challenging. Although clinical guidelines recommend arteriovenous fistula as the optimal type of vascular access, older hemodialysis patients have significantly worse fistula outcomes. For those whose created fistulas are not usable in a timely matter, advantages of fistula attempts are greatly compromised. Few studies have tracked fistula development and maintenance as an integrated care process in older hemodialysis patients. Evidence on the association of age and fistula outcomes is scarce in the literature. There is also a call to identify older patients who are more likely to benefit from a fistula placement.

The first contribution of this dissertation is the description of arteriovenous fistula development as a process of care from the initial step of fistula placement to achieving continuous fistula patency. We examine the proportion, timing, and geographic variability of fistula construction and outcomes among older hemodialysis recipients and find only a small proportion of them have completed the sequential stages of fistula care in the United States. There is a need to address disparities in fistula care continuum to improve fistula outcomes.

The second contribution of this dissertation is the precisely estimation of the effect of age on arteriovenous fistula construction and outcomes. We find increasing age is significantly associated with lower probability of fistula placement and maturation but not fistula primary and secondary patency loss. We conclude the likelihood of fistula maturation should be the most important consideration for vascular access planning in older dialysis recipients and fistula might not the best vascular access option for patients approaching eighty years old.

The third contribution of this dissertation is the externally validation of the Lok's risk equation for fistula primary failure which has achieved good prediction accuracy previously. We show the Lok's model is invalid to predict fistula primary failure in the U.S. older hemodialysis patients. Finally, we use random survival forests to identify important predictors for fistula maturation and find patient's gender might be considered as the most important predictor for fistula maturation.

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DEDICATION

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"I can do all this through Him who gives me strength." Philippians 4:13

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Chronic kidney disease (CKD) is a condition in which the kidney is damaged to an extent such that it no longer has a capability to filter blood. The last stage (stage 5) of CKD is called End Stage Renal Disease **(**ESRD). It is a permanent state of advanced kidney failure that requires kidney replacement therapy (KRT, dialysis or kidney transplantation) to sustain life. Diabetes, hypertension, cardiovascular disease, and genetic defect are common risk factors for CKD. CKD and ESRD can lead to premature death and decreased health-related quality of life for those affected. In addition, approximately a quarter of Medicare budget was spent on treating CKD and ESRD patients.[1] The Healthy People 2020 identified CKD as one of nationwide health improvement priorities.[2] Care of CKD and ESRD has significant public health and clinical implications. It represents a great opportunity to improve patient outcomes and reduce healthcare costs. It was estimated that annually, more than 12,000 life years could be saved if a current practice meets the targets in clinical guidelines in six major areas of ESRD care, including dialysis dose, phosphate control, anemia treatment, serum albumin correction, interdialytic weight gain, and vascular access use.[3]

PART ONE: END STATE RENAL DISEASE AND HEMODIALYSIS

Incidence and Prevalence of End Stage Renal Disease and Hemodialysis

The US ESRD incidence rate has increased substantially since the 1990s, before leveling in the 2000s.[4] In 2013, however, the rate began to rise again. In 2015, there were 124,114 newly reported cases of ESRD and the crude incidence rate was 378 per million population (PMP).[4] With an escalating incidence rate and aging of the U.S. population, the ESRD prevalence has grown continuously from the 1990s.[4] At the end of 2015, the ESRD population had increased to 703,243 patients. The crude prevalence rate had reached 2,128 PMP.[4]

Of all U.S. ESRD patients, over 440,000 (63%) are maintained on hemodialysis.[4] Only 30% live with a functioning transplanted kidney, and 7% are treated by peritoneal dialysis.[4] Among hemodialysis patients, an overwhelming majority of them (98%, over 430,000 patients) use in-center hemodialysis, while only 2% dialyze at home.[4] The distribution of incident treatment modalities follows the same pattern. In 2015, for example, a dominant portion of the incident ESRD patients (87%) initiated their KRT with hemodialysis. Only 2.5% of them received a kidney transplant and 9.6% started with peritoneal dialysis.[4]

Mortality and Morbidity of End Stage Renal Disease and Hemodialysis

The past decade has witnessed a significant decline in ESRD mortality and hospitalization rate. The adjusted mortality rate of the ESRD population after controlling for the population characteristics decreased by 28% from 189 per 1,000 person-years in 2001 to 136 in 2015.[4] In 2015, the adjusted mortality for hemodialysis patients, peritoneal patients, and transplant patients were 169, 159, and 29 per 1,000 person-years, respectively.[4] The adjusted rate

of hospital admission for hemodialysis and peritoneal dialysis patients has declined 19%, from 2.1 per patient year in 2006 to 1.7 in 2015.[4] In 2015, hemodialysis patient hospitalizations due to cardiovascular events and for infections were 0.46 and 0.44 per patient year.[4]

Medicare Expenditures on End Stage Renal Disease and Hemodialysis

Since the October of 1972, Medicare has extended its coverage to all ESRD patients and created the first universal disease-based health care system in the U.S..[5] Most patients with ESRD are eligible for Medicare coverage 90 days after initiation of their kidney replacement therapy. ESRD care has poses a significant national health care burden. Although comprising less than 1% of the Medicare population, the ESRD population consumed 7% ($34 billion) of the total Medicare expenditures in 2015.[4] When adding an extra $64 billion of CKD costs, total Medicare spending on both CKD and ESRD was over $98 billion.[4] In 2015, the Medicare spending for hemodialysis population was $26.7 billion in total and $88,195 per patient per year (PPPY).[4] While the PPPY for hemodialysis patients remains stable, the escalated costs are likely to be attributed by the growth of the prevalent hemodialysis population.[4]

PART TWO: VASCULAR ACCESS

Types of Vascular Access for Hemodialysis

A well-functioning and reliable vascular access is essential for efficient hemodialysis. The three basic access types used by most hemodialysis patients are arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC) (**Figure 1**). An AVF is a naïve connection of an artery to a vein created by a vascular surgeon on patient's forearm (radiocephalic) or upper arm (brachiocephalic and brachiobasilic). After placement, a typical AVF needs at least 2 to 3 months to achieve vein enlargement and an increase in tissue mass to be usable for dialysis. An AVG is similar to an AVF; it uses a looped, plastic tube as a connection. A patient can usually use an AVG 2 to 3 weeks after placement. A CVC is a tube inserted into a vein in patient's neck, chest, or leg, usually for short-term use. Observational studies have demonstrated that AVFs, once functional, exhibit greater longevity, are less prone to infection, and are also associated with reduced mortality and lower cost, compared with AVGs and CVCs.[6,7] CVC, on the contrary, is deemed the most inferior of all three access types and should only be used as a temporary access for hemodialysis. It is related to substantially elevated rates of infection[8,9] and increased all-cause mortality.[10,11] However, it might be the only choice for patients with a limited life expectancy, or when the surgical creation of an AVF is dangerous because of the risk of cardiac failure.[12] AVGs tend to require more interventions and are more likely to fail after successful use compared to AVFs, but they have a higher initial rate of successful use compared to AVFs and lower infection rates compared to CVCs.[13] Studies have shown when rates of primary failure are considered, AVGs do not differ significantly from AVFs in either functional longevity or all-cause mortality.[14,15,16]

"Fistula First" Initiative and Clinical Guidelines for Vascular Access

In 2003, the Centers for Medicare and Medicaid Service (CMS) launched the National Access Improvement Initiative (NVAII), later renamed as the Fistula First Breakthrough Initiative (FFBI).[6] The goal of FFBI is to achieve functional AVF use in greater than 65% of hemodialysis patients and to reduce CVC utilization in less than 10% of hemodialysis patients. In collaboration with the 18 national ESRD Networks, CMS promulgated the FFBI goal through its Clinical Performance Measures (CPMs) and established Quality Improvement and Patient safety (QIPS) rules with financial incentives to improve AVF use. Dialysis units that do not achieve the AVF target will face reimbursement penalties.[17] The 2006 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK/KDOQI) Clinical Practice Guidelines for vascular access echoed "Fistula First" with its similar recommendations.[18] To emphasize the importance of CVC avoidance, CMS also updated the FFBI and renamed it "Fistula First Catheter Last" (FFCL), highlighting the needs to establish AVF or AVG and reduce the use of CVC. [19]

Prevalence and Incidence of Each Type of Vascular Access

Arteriovenous Fistula (AVF)

The FFCL policy has made dramatic progress; it successfully raised prevalent AVF use in the U.S. from 24% in 1997[20] to 63% in 2016.[4] However, the incident rate of AVF use at the initiation of dialysis has not been changed significantly. The proportion of patients using an AVF for vascular access at dialysis initiation was 17% in 2015,[4] compared to a lesser 12.3% in 2005.[21] Similarly, the rate of initiating dialysis with either an AVF or a maturing AVF has only increased

slightly from 29% to 33% over the same period of time.[4,21] From a longitudinal prospective, rate of AVF utilization in U.S. rises gradually after dialysis. At dialysis initiation, 17% of patients use AVF.[4] This rate turned into roughly 42% at 6 months and reaches 60% at one year.[4]

Arteriovenous Graft (AVG)

From 1997 to 2015, the prevalent AVG use has consistently dropped from 49%[22] to 17.6%.[4] In the middle of 2016, only 3% of hemodialysis patients used an AVG for dialysis initiation, although this number increased to 15% a year after initiation.[4]

Central Venous Catheter (CVC)

FFCL has effectively reduced prevalent CVC use. From 1997 to 2015, CVC presence in hemodialysis population has been cut from 27%[22] to 19.5%.[4] In spite of the reduction in CVC use, approximately 80% of patients are still using a CVC to initiate dialysis in 2015, which has not been changed significantly since 2005.[4]

In summary, the trend of vascular access use in the past decade has reflected a marked increase in prevalent AVF and decrease in prevalent CVC use. However, placement and use of AVG have been diminished, since there is now a trend of using CVC as a "bridge access" to obtain a usable AVF.

PART THREE: FISTULA CARE

Fistula Care Continuum

The continuum of AVF care has three distinct processes, with a requirement that each of the three must be successfully overcome in order to reach a useable AVF. First, a patient must be referred to a vascular surgeon and an AVF must be created. Second, the AVF must mature sufficiently in order to be used repeatedly to deliver dialysis. Third, once the AVF has matured, it needs to remain patent for a prolonged period of time. Suboptimal delivery of any of these three processes of care will result in a lower rate of AVF utilization.

AVF Placement

To obtain a usable AVF at dialysis initiation, an AVF must be placed early to allow sufficient time for maturation and revision. The KDOQI guidelines emphasize that patients with stage 4 CKD (GFR<30 ml/min/1.73 m^2) should be consulted with options for KRT and be referred to permanent vascular access placement if the patient agrees to proceed with hemodialysis. Ideally, such a patient should have an AVF placed 6 months before dialysis to avoid CVC use. Nevertheless, this timeline is achieved in only a minority of patients. Merely 30% of AVFs placed in U.S. prevalent hemodialysis population are created prior to initiation of dialysis.[4] Of the AVFs created pre-dialysis, nearly half of them (47%) are created at the time approaching (within 90 days of) dialysis initiation.[4] Consequently, over 80% of patients in the U.S. initiate dialysis with a CVC, which serves as a "bridge access", until an AVF or an AVG has been placed and is ready to be used.[4]

These disappointing statistics of late AVF/AVG placement might be attributed by several reasons. Firstly, more than a third of incident ESRD patients in the U.S. received little to no pre-ESRD nephrology care.[4] These patients are more likely to have their AVF/AVG placement postponed and instead initiate dialysis with a CVC. This is evidenced by the fact that 35% of patients who initiated dialysis with a CVC had no pre-ESRD care.[4] Secondly, the glomerular filtration rate (GFR) trajectory is difficult to project and varies with age and comorbid conditions. Therefore, it is very challenging to accurately predict the likelihood and timing of dialysis initiation. Despite tight nephrology follow-ups, for instance, 20 - 40% of patients with CKD experienced sudden GFR drop that led to urgent dialysis initiation.[23] On the contrary, 18% of CKD patients did not progress to ESRD until two years after AVF placement, and those placed AVFs were wasted.[24]

AVF Primary Failure, Maturation, and Assisted Maturation

Whereas the definitions of AVF maturation vary greatly in literature, AVF maturation generally is judged by whether or not AVF is ready to provide an adequate delivery of blood to the dialyzer. It is expected that once an AVF is formed, increase in blood flow will progressively dilate blood vessels and thicken vessel walls to an extent as to sustain repeated cannulation for dialysis.[25,26] In 2011, The North American Vascular Access Consortium (NAVAC), a group of multidisciplinary experts from the U.S. and Canada, published common standards for terminology in the field of vascular access. They defined AVF maturation as that an AVF can be used with two-needle cannulation for two-thirds or more of all prescribed dialysis for one month.[27] The National Institute of Health Hemodialysis Maturation (HFM) Study in 2014 described AVF maturation as "with 2 needles for 75% of dialysis sessions over a continuous 4-

week period and either: (1) 4 consecutive sessions during the 4-week period in which 2 needles are used and the mean dialysis machine blood pump speed is ≥300 mL/min. or (2) a measured single-pool Kt/V≥1.4 or urea reduction ratio >70% during any session in which 2 needles are used within the 4-week period".[28] In addition to proving adequate delivery of blood, the definition of AVF maturation must have a time component since longer follow-ups allow more AVF to mature. The HFM study defined AVF maturation within 9 months of AVF creation or within 8 weeks of dialysis initiation.[28]

NAVAC defined AVF primary failure as an AVF immediate fails within 72 hours of surgery (immediate failure), or is not suitable for dialysis despite interventions (radiologic or surgical) by the three (early suitability failure) to six months (late suitability failure) following its creation.[27] As compared to primary failure, failure-to-mature does not include early technical failures such as intraoperative thrombosis.

A substantial proportion of newly placed AVFs failed to mature and thus required additional interventional procedures to promote maturation ("assisted maturation"). As the USRDS data report noted, of AVFs placed between June 2014 and May 2015, 36% of failed to mature sufficiently for dialysis.[4] One meta-analysis which included studies published in 2000 or later, the AVF primary failure rate was 23%.[29] In one cohort study of elderly Medicare beneficiaries who initiated hemodialysis from 2010 to 2011, 40-63% of placed AVFs underwent one or more interventional procedures to assist maturation.[30] These procedures usually include angioplasty or surgical revision of an anastomotic stenosis, ligation or coiling of large accessory veins, or superficialization of excessively deep AVFs. Interventional procedures consume radiological and surgical resources, and often lead to prolonged period of dialysis dependency on CVC, which is associated with substantially elevated rates of infection[8,9] and mortality.[10,11]

Moreover, biological changes caused by these procedures may engender certain detrimental effects, which leads to suboptimal AVF outcomes. Studies have shown that AVFs which experienced pre-maturation intervention have shorter patency and are more likely to require post-maturation interventions to maintain functionality compared to those that matured without assistance.[31] There have been limited published information on differential impact of interventional procedures by type and frequency on AVF patency after maturation. A small study of 77 hemodialysis patients who had an AVF placed and received subsequent interventional procedures (55 patients received endovascular vs. 16 received surgical revisions) indicated that there was no difference in AVF patency when comparing patients who had endovascular verse surgery to promote maturation.[32]

AVF Patency

Many measurements of AVF long-term outcomes after maturation are clinically meaningful. But the most frequently used in clinical research could be categorized into descriptions of access patency (primary, cumulative, or functional) and patency loss. Primary patency, also known as unassisted patency, is the time from AVF creation until any intervention to maintain or restore blood flow. Loss of primary patency denoted a requirement for any intervention after successful use of AVF. Secondary patency, also called assisted or cumulative patency, is the time from AVF creation until the AVF can no longer be used for dialysis and the associated problem cannot be corrected by any intervention. Functional patency (primary or secondary), however, is different from the above two types of patency in that it counts time from AVF maturation or successful cannulation instead of AVF creation. For example, AVF primary functional patency is defined as the time from AVF maturation until first revisions. In addition,

some studies examine AVF survival after certain procedures promoting maturation. For example, postintervention primary patency is the time from the index procedure until the next AVF intervention.

A few studies have examined AVF post-maturation patency. Patency rates can vary greatly by patient population, previous access history, follow-up time, and the year of study. For example, analysis of a cohort study of 293 patients at Mayo Clinic with an AVF placed found that 3-, 6-, 12-, and 18-month primary patency rates were 67%, 50%, 41%, and 30%, and secondary patency rates were 92%, 86%, 77%, and 73%, respectively.[33] One study evaluating vascular access outcomes in 9,458 elderly Medicare patients who initiated hemodialysis from 2010 to 2011 reported that primary and secondary patency rates were 73% and 82%, respectively, a year after maturation.[34]

Costs Associated with Fistula

Thamer et al. has recently published a paper on Medicare expenditures on AVF.[30] In their paper, they followed three groups of patients that initiated hemodialysis from 2010 to 2011 and examined their vascular access-associated costs by AVF outcomes. The first cohort includes patients who initiated hemodialysis with a matured AVF; the second, the patients who initiated hemodialysis with a maturing AVF; and the third, patients who initiated hemodialysis with a CVC. The results of their study showed that PPPY costs 2.5 years after AVF creation were $7,871, $13,282, $17,808, and $31,630 respectively, for patients whose AVFs maintained primary patency, patients whose AVFs experienced primary patency loss, and secondary patency loss in year 1, for AVFs that were not used. They also showed that the annual Medicare expenditures on vascular access-related services from 2011 to 2013 sum up to $2.8 billion, which

is ~12% of all ESRD spending. In addition, the costs of AVF placement and interventions are not trivial. It was estimated that the fistula costs per patient per year in the first two and half years after AVF placement were $13,282 for patients whose AVFs had primary failure and $30,818 for patients whose AVFs were abandoned.

Disparities in Fistula Care

Significant disparities exist in likelihood of AVF placement, maturation, and patency.

Racial Disparities

African Americans are less likely to use an AVF. In spite of the overall increase in AVF use among U.S. hemodialysis patients, the gains have been less pronounced in blacks than in whites. AVF use is lower in blacks than whites in almost all the 18 dialysis networks.[7] An analysis of 1,824 hemodialysis patients enrolled in the Hemodialysis (HEMO) Study between 1995-99 reported AVF use in 27.7% of blacks vs 45.5% of non-blacks.[35] Blacks were 36% less likely to use an AVF even after controlling for age, gender, obesity, cardiovascular disease, income, education, and insurance status. A subsequent analysis of U.S. patients initiating dialysis with a CVC in 1999-2003, observed racial disparities in conversion to a permanent access during the first 3 months of hemodialysis.[36] As compared to white males, black females and black males were 75% and 35%, respectively, more likely to maintain CVC use. Finally, a national survey for 2012-14 revealed AVF use in 58% of black hemodialysis patients vs 70% of whites.[22] The racial differences were particularly striking in black women: 75% AVF use in white men, 65% in black men, 65% in white women, and 50% in black women. In other words, the absolute rate of AVF use was 15% lower in black women than white women. Notably, racial disparities in the

frequency of AVF use between blacks and whites begin at dialysis initiation and increase over time after initiation of hemodialysis. At dialysis initiation, the proportion of blacks and whites using an AVF is 15.4 vs 17.7%, and the disparity increases progressively during the first year on dialysis (22.5 vs. 26.2% at 3 months; 40.1 vs. 47.2% at 6 months; 52.8 vs. 61.0% at 9 months; and 58.8 vs. 67.8% at 1 year). Thus, the absolute difference in AVF use between blacks and whites increases from 2.3% at hemodialysis initiation to 9.0% at 1 year, indicating processes of care to achieve an AVF likely differ substantially between the races.[37]

Gender Disparities

The substantial gender disparity in AVF maturation among hemodialysis patients has been observed repeatedly in many studies. For example, an analysis of 1,824 patients enrolled from 1995 to 1999 in the HEMO Study reported AVF use in 22.4% of female patients vs. 46.3% of males.[35] Similarly, the USRDS report from 1999 documented a strikingly lower rate of AVF use in prevalent female vs. male hemodialysis patients in each of the 18 U.S. dialysis networks, with the absolute rate being approximately 20% lower in females.[7] Though the overall proportion of patients dialyzing with an AVF has increased greatly in both genders following the 2003 Fistula First Initiative,[19] the gender discrepancy persists. The Dialysis Outcomes Practice Patterns Study (DOPPS) of prevalent U.S dialysis patients from 2010 to 2013 reported a lower use of AVFs in women than in men for both black patients (50 vs. 65%) and for non-blacks (65 vs. 75%).[22] Most recently, the 2017 USRDS report documented AVF use in 55.2 % of female patients vs. 68.8% of males, an absolute difference of 13.6%.[38] The gender gap in AVF use persists a full year after dialysis initiation. At 6 months and one year, females had 13.3% and 14.7% lower proportion of AVF use as compared to males.

Whereas the rate of AVF use is distinctly lower in females as compared to male patients, studies have yielded conflicting results in regard to the association of gender and AVF post-maturation outcomes. A meta-analysis of 37 early reports published from 1970 to 2002 concluded that females have similar AVF primary failure rates, and primary and secondary potencies as males.[39] However, a study of 2,247 dialysis patients with a newly placed AVF from the Dialysis Morbidity and Mortality Study (DMMS) from 1997-99 reported that the risk of AVF primary failure was 18% greater in females than in males. The rate of AVF secondary failure, however, did not differ significantly between females and males.[40] In particular, a single center study observed that females experienced a greater rate of AVF failure than males, despite routine preoperative mapping and more frequent interventions in females to promote maturation.[41] The association of female sex and higher rate of AVF primary failure was also confirmed by a multi-center study of 395 patients with AVF placement from 2004 to 2006.[42] Similarly, two newer, small studies have examined the impact of gender on AVF assisted maturation and outcomes. The first study included 173 hemodialysis patients who had a new AVF placed between 2005 and 2007 and did not experienced an AVF primary failure.[31] This study showed that female gender is associated with higher proportion of interventions before AVF maturation. The second study followed 289 patients that initiated hemodialysis with a CVC from 2006 to 2011 and had a subsequent AVF placed. [32] The evidence displayed that female patients are more likely to require interventional procedures to facilitate maturation compared with male patients. However, gender is not significantly associated with secondary functional patency. In both studies, assisted access maturation was associated with higher rates of access abandonment and an increased frequency of interventions to maintain access patency after maturation.

Age Disparities

As pointed out by multiple studies, older age is an independent risk factor associated with a lower rate of AVF maturation and inferior AVF long-term outcomes.[43,44,45] Nationwide, the rate of AVF use is lower among patients aged 75 years or older (59%) as compared to those aged 65 and younger (65%).[4] One meta-analysis of AVF outcomes from 10 studies concluded that elderly patients aged >50 to >70 had significantly reduced one-year primary and secondary patency and maturation rates.[46] The odds of AVF primary failure in elderly patients aged >50 to >70 were 1.5 times of those of non-elderly at 12 months and 1.4 times at 24 months. In an economic study examining the resources and costs associated with creating and maintaining AVFs, 40-63% of functional AVFs placed in the U.S. elderly between 2011 and 2013 required therapeutic interventions to facilitate maturation.[30] A total of 71-86% of these AVFs required post-maturation interventions to maintain their functionality during the first year after placement. AVFs placed in older hemodialysis patients are more likely to take longer time to mature. As noted in the 2017 USRDS report, a quarter of AVFs placed in surviving hemodialysis patients aged 65 and older takes more than 6 months to mature.[4]

Comorbid Disease Disparities

Comorbid conditions can have a major impact on the prevalence of patients dialyzing with AVFs. Early studies showed a difference in the prevalence of AVF maturation and AVF long-term outcomes between patients with and without diabetes. For example, the Dialysis Outcomes and Practice Patterns Study noted that among the 3,882 American and 2,597 European prevalent hemodialysis patients from 1996-2000, those without diabetics were 32% more likely to use AVF compared to patients without diabetes.[20] The DMMS study of 2,247 dialysis patients with a newly placed AVF from 1997-99 noted that patients with diabetes had 10% increased risk

of primary failure, compared to patients without diabetes. [40] But diabetes is not associated with an increased risk of secondary failure. Changes of practice patterns in recent years have gradually closed up the gaps in AVF use among diabetic patients. A single-center analysis of 195 patients suggested that vascular mapping could greatly improve the rate of AVF placement in diabetic patients through careful preoperative vessel imaging and AVF site selection.[47] In this study, there was only a 6% difference in the rate of AVF placement between diabetic and non-diabetic, and AVF outcomes were similar regardless of the presence of diabetes. A multi-center study of 395 patients with AVF placement from 2004 to 2006 suggested that diabetes was significantly, but marginally, associated with primary function patency loss.[42] Another single-center study of 748 patients also demonstrated that increased use of AVFs and satisfactory AVF outcomes in diabetic patients could be achieved by proper preoperative evaluation, exclusive use of native vessels and a variable surgical approach.[48] Most recently, the 2017 USRDS report documented comparable rates of AVF use in prevalent and incident hemodialysis patients with diabetes and the general hemodialysis population (16.9% vs 17% and 63.4% vs 63%).[4]

Geographic disparities

Practice patterns can have a major impact on the prevalence of patients dialyzing with AVFs. The DOPPS study reported that AVF use in 2013 varied greatly across US dialysis facilities, ranging from 54% to 84%.[22] Two early reports found substantial geographic variations in the prevalence of AVF use. Higher AVF use was found in the U.S. Northeastern region while the South had lower rates of AVF use.[35,49] In both reports, these geographic differences persisted even after the adjustment of multiple demographic factors and co-morbid conditions. Similarly,

variations in AVF use were also reflected in more recent national data, that the Northwest region displays the highest rate of prevalent and incident AVF use.

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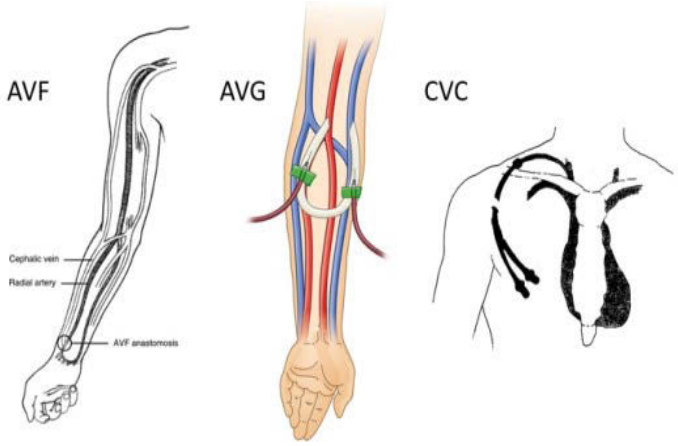
Figure 1. Three type of hemodialysis vascular access: arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC).


AVF
Cephalic vein
Radial artery
AVF anastomosis
AVG
CVC

CHAPTER TWO

ARTERIOVENOUS FISTULA CARE CONTINUUM IN OLDER ADULTS UNDERGOING HEMODIALYSIS

ABSTRACT

Background: Arteriovenous fistula **(**AVF) development could be viewed as a care process from the initial step of AVF placement to achieving the goal of continuous AVF patency. Our study aims to evaluate the proportion, timing, and geographic variability of AVF development and outcomes in the U.S. older hemodialysis recipients.

Methods: We assembled a retrospective cohort of incident hemodialysis adults aged 67 years and older who initiated dialysis (43,851), had an AVF placed (14,892), or had the placed AVF matured (7,528) from the United States Renal Data System. We determined rates of AVF placement, maturation, and patency loss in total, by month, and by geographic region and ESRD network. The incidence rates of pre- or post-maturation interventions were reported. Logistic regression model was used to examine the association of geographic regions with AVF outcomes, adjusted by age, gender, race, BMI, functional status, and comorbid score.

Results: Only 13% of older patients who initiated dialysis with a CVC completed the three processes of AVF care and maintained functionality 2 years after AVF maturation. The ranges of pre- and post-maturation interventions rates were 0 to 8.4 and 0 to 1.1 per patient per month. The median time from dialysis initiation to AVF placement and from placement to maturation was 2 months (IQR: 1-4) and 5 months (IQR: 4-7). The median AVF primary and secondary functional patency was 2 months (IQR: 1-5) and 3 months (IQR: 2-7). There existed moderate geographic variations in AVF placement and patency. Geographic difference in AVF maturation was not evident.

Conclusion: A small proportion of older incident hemodialysis patients have AVF placed, matured, and remained patent. These findings highlight the critical need for early AVF placement in proper candidates and addressing geographic disparities in older dialysis patients.

INTRODUCTION

Current clinical guidelines recommend a well-functioning arteriovenous fistula (AVF) as the preferred form of vascular access for hemodialysis.[1] To achieve a useful and lasting AVF, an AVF must be placed, mature sufficiently, and remain patent to deliver dialysis. Ideally, if the three processes are completed promptly, patients are able to avoid or reduce use of a central venous catheter (CVC) for dialysis, which is associated with increased all-cause mortality.[2,3,4]

Annually more than 50,000 patients aged 65 and older with the end stage renal disease (ESRD) initiate hemodialysis in the United States.[5] Older adults are also the fastest growing segment of the prevalent dialysis population due to the escalating rate of ESRD incidence, aging of the U.S. population, and prolonged survival on dialysis. Studies show older age is significantly associated poor AVF outcomes. Nationwide, the prevalence of AVF use was lower in patients over 75 years (61%) as compared to those 65-74 (64%) and 45-64 (67%).[5] In the meta-analysis of AVF outcomes from 10 studies which defined elderly from >50 to >70 years old, the rate of AVF maturation failure was significantly higher in elderly compared with that in nonelderly.[6] In addition, AVFs placed in older adults are likely to take longer time to mature. As noted in the 2017 USRDS report, the median time from AVF placement to maturation is 116 days in patients aged 65-74 as compared to 109 days in patients aged 45-64.[5] Despite suboptimal AVF outcomes in this growing population, few studies have tracked AVF development and maintenance as an integrated care process. Our study aims to evaluate AVF care as a continuum model as the proportion of individuals, the timing of achievement, and the geographic variability at each stage of AVF development and maintenance in the U.S. older hemodialysis recipients. It allows us to identify the pivotal gaps and obstacles in the AVF care that impact the ultimate AVF use.

METHODS

Data Sources and Study Population

Our primary data source was derived from the 2010-2014 USRDS standard analytic files (SAFs). **Figure 1** demonstrated development of our three study cohorts. Cohort 1, the hemodialysis cohort, included 43,851 incident patients aged 67 years and older who initiated dialysis through a CVC between 7/1/2010 and 6/30/2012. To ensure that the CVC was the only vascular access present at the start of hemodialysis therapy, patients were excluded if they: (1) were using an AVF or AVG or had an AVF or AVG placed but were awaiting maturation at hemodialysis therapy initiation, as reported in the Medical Evidence Form; (2) underwent AVF or AVG surgery in the 2-year pre-ESRD period, as assessed by Current Procedural Terminology-4 (CPT-4) procedure codes of 36818, 36819, 36820, 36821, and 36825 for AVF and 36800, 36810, and 36830 for AVG. From the hemodialysis cohort (cohort 1), we further identified two subcohorts. Cohort 2, the AVF placed subcohort, included 14,569 patients who had AVF placements within 6 months after dialysis initiation. Cohort 3, the AVF matured subcohort, included 7,301 patients whose AVFs matured within 6 months after placement.

Variables of Interest

The primary outcomes of this study were AVF placement (cohort 1), AVF maturation (cohort 2), and primary and secondary patency loss (cohort 3). We identified AVF placement by using CPT-4 codes as listed above. AVF maturation was ascertained by using the first vascular access modifier code 'V7' reported from the institutional details claims file or the first AVF used with two needles reported from the Crownweb clinical file. Patients were considered to have assisted maturation if they underwent an intervention prior to maturation, and to have unassisted

maturation if they did not undergo such an intervention. Codes used to identify intervention procedures including angioplasty, thrombectomy, revision, ligation, banding, and embolization of accessory veins were listed in **Table S1**. We defined AVF primary patency loss as the first revision procedure after maturation. We defined AVF secondary patency loss (abandonment) as 3 consecutive months of CVC use or a new vascular access placement. Primary and secondary functional patency was ascertained as the time from AVF maturation to primary patency loss or abandonment, respectively. Cohort 1 was followed for 3 years from dialysis initiation. Cohort 2 was followed for 2 years from AVF placement. Cohort 3 was followed for 2 years from AVF maturation. Patients who died, switched to peritoneal dialysis, or received a kidney transplant during the follow-up period were identified by using the USRDS death file, the transplant file and dialysis institutional claims file, respectively.

We extracted patient demographics, residential region (New England, Mid-Atlantic, West, Southwest, Midwest, and South), BMI, functional status (amputation, inability to ambulate or transfer, needs assistance with daily activities, or institutionalized), lab values (hemoglobin, serum albumin, and glomerular filtration rate), primary cause of renal failure, pre-dialysis nephrology care, and facility provider ID from the Medical Evidence Form. In addition, 2-year pre-ESRD CMS Medicare claims were used to identify major comorbidities conditions. ESRD network number, facility's profit status and hospital association were ascertained from the facility file.

Statistical Analysis

We summarized baseline patient characteristics and facility practice patterns for each study cohort. Rates of AVF placement, maturation, and primary and secondary patency loss were

determined in total and by month. The incidence rate of pre- or post-maturation interventions was calculated as number of interventions divided by time needed to achieve maturation or length of secondary functional patency. We also examined distribution of AVF outcomes by ESRD network. Logistic regression model was used to examine geographic regions with AVF outcomes, adjusted by age, gender, race, BMI, functional status, and comorbid score. Data management and analyses were performed using SAS (version 9.4; SAS institute, Cary, NC).

RESULTS

Baseline Characteristics

Table 1 lists patient characteristics in three study cohorts. Cohort 1 included 52.4% male, 75.4% White, 15.8% aged 85 and older, 65.3% diabetic, 74.3% hypertensive and 63.5% with coronary artery disease. The two subcohorts, cohort 2 and 3, consisted of slightly higher proportions of males (54.5% and 60.1%), lower percentages of Black (18.5% and 16.9%), and lower proportions of patients aged 85 and older (13.8% and 13.2%). Patients in three cohorts carried heavy comorbid burdens and had low functional status. In the aspect of care patterns, over 80% of patients dialyzed in a for-profit facility and 48-55% had pre-dialysis nephrology care.

Fistula Care Continuum

Nationally, among 100 older adults who initiated hemodialysis with a CVC, 39 of them had an AVF placed within 3 years, 27 of them had their placed AVF matured within 2 years after placement, and 13 of them maintained secondary patency within 2 years after maturation (**Figure 2**).

AVF Placement from the Hemodialysis Cohort

Of 43,851 patients who initiated hemodialysis with a CVC in cohort 1, 39.4% of them had an AVF placed within 3 years of dialysis initiation and 40.8% died, received a kidney transplant, or transferred to peritoneal dialysis. The majority of AVFs (83.8%) were placed within 6 months after dialysis initiation and 60.5% were placed from the 2nd to 4th month. The 3rd month after dialysis initiation has the highest placement rate (24.0%). The median time from dialysis initiation to AVF placement was 2 months (IQR: 1-4) (**Figure 3A**).

AVF Maturation from the AVF Placed Cohort

Among 14,892 patients in cohort 2 who had an AVF placed within 6 months of dialysis initiation, 68.9% of them had their AVFs matured and 20.3% died, had a kidney transplant, or transfer to peritoneal dialysis without using AVFs. **Figure 3B** showed distribution of AVF maturation in each month after AVF placement. The highest proportion of AVFs matured in the 4th month after placement (21.1%). Within 6 months of AVF placement, 73.3% of AVFs matured. The median time to reach maturation was 5 months (IQR: 4-7) and 25% of patients took 7 months or more to use their AVFs (**Figure 3B**).

In cohort 2, over half of the matured AVFs (55%) required one or more interventions to facility maturation (i.e. assisted maturation). The distributions of number and incident rate of pre-maturation interventions were highly screwed: the number varied from 0 to 42 with the median of 1 (IQR: 0-2); the incident rate varied from 0 to 8.4 per patient per month with the median of 0.1 (IQR: 0-0.3) (**Table 2**). Approximately 1% of the matured AVFs had ≥ 9 interventions to assist maturation.

AVF Primary Patency Loss from the AVF Matured Cohort

Of 7,528 matured AVFs in cohort 3, 75.2% of them experienced primary patency loss. Approximately 10.9% continued using AVF without any revision and 13.9% died, had a kidney transplant, or transferred to peritoneal dialysis within 2 years after maturation. A majority of primary patency loss (80.4%) occurred in the first 6 months. It was most likely to occur in the first month (32.6%). The median primary functional patency was 2 months (IQR: 1-5) (**Figure 3C)**.

AVF Abandonment from the AVF Matured Cohort

A total of 25.2% of matured AVFs were abandoned within 2 years after maturation. Approximately 46.4% of patients with matured AVFs continued to use their AVFs for dialysis and 28.4% of patients died, had a kidney transplant, or transferred to peritoneal dialysis. AVF abandonment occurred most frequently in the 3rd month of dialysis (31.5%). Over 74.8% of AVFs were abandoned at the end of 6 months of dialysis. The median secondary functional patency was 3 months (IQR: 2-7) (**Figure 3D**).

Among the AVFs which maintained secondary patency, the total number of post-maturation revisions ranged from 0 to 27 with the median of 2 (IQR: 1-5). The incident rate of access revisions ranged from 0 to 1.1 per patient per month with the median of 0.1 (IQR: 0-0.2) (**Table 2**). Approximately 5% of patients experienced ≥ 10 revisions to maintain AVF functionality.

Geographic Variability

There existed moderate variations in AVF placement and patency loss by geographic region and ESRD network (**Figure 4 and 5**). Especially, the Mid-Atlantic region had the lowest rate of AVF placement (35.6%) and the highest rate of AVF primary patency loss (84.2%). Accordingly, network 2, 4, and 7 had the lowest rate of AVF placement (33.0%, 30.5%, and 33.6%, respectively) and network 2, 4, and 5 had the highest rate of AVF primary patency loss (84.6%, 83.6%, and 81.7%, respectively). This statistical significance persisted after adjusting for patient's age, gender, race, comorbid conditions and functional status. On the contrary, the odds of placing AVF in older hemodialysis patients was the highest in the New England area (network 1) (48.0%; adjusted OR 1.63; 95% CI 1.46-1.83).

The West had the lowest rate of AVF primary patency loss (72.3%, adjusted OR 0.59; 95% CI 0.48, 0.71) among all regions. Two highest rates of AVF primary patency loss were 65.3% in network 16 (Northwest states) and 68.5% for network 18 (Southern California). The New England, South and Southwest had higher abandonment rate than the other three regions. The rate of AVF abandonment was 32.8% in network 2 (New York) and 30.6% in network 16 (Northwest states). AVF maturation, however, was not significantly different among geographic regions except the South a borderline significance in maturation rate (67.5%; adjusted OR 0.87; 95% CI 0.77-0.98).

Sensitivity Analyses

In the subset of 2,574 patients who had an intervention during the same calendar month as the AVF maturation, there was uncertainty about whether the intervention occurred before maturation or after maturation since AVF use was reported monthly. Our primary analysis assumed that all interventions occurring during that month of AVF maturation were after

maturation. In sensitivity analysis, we assumed that all interventions during that month of maturation represented interventions to facilitate maturation. The new percentage of assisted maturation was 63.8%, increased from that in the primary analysis (55%). The number of interventions varied from 0 to 53 times with the median of 1 (IQR: 0-3) and the 99th percentile increased to 10. Similarly, the incident rate of intervention increased slightly ranging from 0 to 10.6 times per patient per month with the median of 0.2 (IQR: 0-0.4) (**Table S2**). The percentage of patients experienced primary patency loss decreased slightly from 75.2% to 72.9%.

DISCUSSION

This is the first study to our knowledge that examines the AVF care continuum in a national sample of older hemodialysis recipients. Our study demonstrates only 13% of older patients who initiated dialysis with a CVC successfully completed the three process of AVF care, and maintained functionality 2 years after AVF maturation. A total of 55% the maturation was facilitated by one or more interventions. AVF functionality was also sustained by frequent revisions. The median time from dialysis initiation to AVF placement and from placement to maturation was 2 months (IQR: 1-4) and 5 months (IQR: 4-7). The median AVF primary and secondary functional patency was 2 months (IQR: 1-5) and 3 months (IQR: 2-7), respectively. There existed moderate geographic variations in AVF placement and patency. Geographic difference in AVF maturation was not evident.

Our analyses reveal a surprising low number of patients had an AVF placed 3 years after dialysis initiation. Results of our study reflect even though the goal of "Fistula First", that is, the AVF use in 65% of the prevalent hemodialysis patients, has been achieved, it is achieved because over 1/3 of patients (39% in 3 years) died while dialyzing with a CVC and these patients are no longer counted in the prevalent hemodialysis population. Current clinical guidelines

recommend referral for access creation 6 months prior to the start of hemodialysis. [2] Nevertheless, merely 33% of the patients initiated dialysis have an AVF placed prior to dialysis.[1] Of the AVFs created pre-dialysis, nearly half of them (47%) are created at the time approaching (within 90 days of) dialysis initiation.[7] Lack of pre-dialysis nephrology care appears to contribute greatly to low rate of AVF placement.[7] In our study, 33% of the patients without a permanent access placement at dialysis initiation had no or less than 6-month pre-dialysis nephrology care. Not only they miss the opportunity for AVF/AVG placement prior to dialysis, but CVC-associated mortality diminishes their chance to have a permanent access placed once dialysis starts

As mentioned before, it is critical to establish a useful AVF at the early stage of dialysis. Our study proves the great efforts made by the U.S. renal community to construct a functional AVF for older patients at the beginning of their dialysis. Nearly 84% of all AVFs placed in the 3 years occurred in the first 6 months after initiating dialysis. Almost 69% of all maturation and associated pre-maturation interventions also occurred within the first half year of placement. However, because the estimated median time from dialysis initiation to AVF maturation is ~7 months, longer survival is needed for an AVF to mature. Identifying a subset of older hemodialysis patients who have a lower risk for early mortality, e.g. those with younger age, less comorbidities, limited functional status, may allow sufficient time for maturation assist clinical decision-making of AVF placement.

After placement, AVF outcomes were worse than those reported in the pre-"Fistula First" era. Firstly, the 2-year rate of AVF maturation (68.9%) obtained from our study is lower to those reported previously. Al-Jaishi et al., for example, in their meta-analysis of AVF outcomes in elderly hemodialysis patients, reported the rate of primary failure at 12 months was 23%.[6] In

addition, AVFs in this study were matured in an average of 5.6 months, which was substantially longer than other published studies. Rayner et al reported the median maturation time for AVFs was 98 days in US from the Dialysis Outcomes and Practice Patterns Study (DOPPS).[8] Allon et al. showed an average maturation time for AVF was 87 days.[9] The lower rate of AVF maturation and prolonged time to maturation in our study might be explained by changes in practice patterns after "Fistula First" policy. Patients who might not be candidates for AVF placement previously due to their inadequate anatomy are likely to have an AVF placed in the post-"Fistula First" era. Including these patients for AVF placement leads to reduced maturation rate and prolonged time to reach maturation. The results of our study are close to those reported by Biuckians et al. in 2008 that AVF maturation rate was 48% of and the mean time to maturation was 146 days (4.9 months).[10]

Few studies have reported 2-year AVF patency rate in the U.S. older adults. Lok et al. showed the 1- and 5-year AVF secondary patency was 75.1% and 64.7% , respectively, for patients 65 years and older.[11] Lee et al. showed the rate of secondary functional patency at 2 years ranged from 57% to 85% in 173 hemodialysis patients from two academic centers.[12] While our 2-year rate of secondary patency is close to previous estimates, the primary patency rate in our study is much lower. This might be explained by increasing use of surgical and endovascular techniques to maintain AVF patency. Lee et al. showed AVFs required assistance to mature had similar secondary patency but higher frequency of interventions and were more likely to have primary patency loss.[13] When an AVF is created in patients who have inadequate anatomy, it is more likely that an aggressive approach is used to maintain AVF patency to match the "Fistula First" prevalence goal. In our study, 23% of AVFs lost their secondary patency. This demonstrates that even if an AVF is matured and used for dialysis, only 77% were functioning

after 2 years. This may seem acceptable in regards to the KDOQI standards, but if we considered those who did not have an AVF placed and those never achieved a functional AVF, only 13 out of 100 patients initiated dialysis still use an AVF.

Our study indicates geographic disparities in AVF outcomes in the post-"Fistula First" era which have not been reported before. Two analyses reported substantial geographic variations in prevalence of AVF use in the U.S. adult hemodialysis patients before the "Fistula First" policy. Hirth et al. reported the prevalence of AVF use varied considerably from a high of 77% in New England to a low of 15% in the Southeast.[14] Allon et al. reported geographic variations in the prevalence of AVF use among 1,824 U.S. adult patients enrolled in the HEMO Study ranging from 45.3% in the Northeast to 30.6% in the Southeast.[15] It is interesting to notice that the crude rate of AVF maturation is not significantly different by geographic region whereas AVF placement and patency loss are affected by practice patterns.

Our study has several limitations. First, we relied on AVF modifier codes or types of access used on the reported dialysis session to ascertain AVF maturation and patency. Access type reported from the dialysis claim may not reflect the AVF most frequently used for dialysis in the month. These codes were submitted by dialysis facilities for billing purpose and thus likely to be subjected to misclassification bias. Second, we cannot distinguish an upper arm AVF from a forearm AVF since the CPT codes of AVF placement do not provide data on the location of an AVF creation. Third, this study only includes elderly patients (≥67 years) in US and results of this study may not be generalizable to younger dialysis patients or patients in other countries.

In conclusion, low percentage of older incident hemodialysis patients in the U.S. have successfully completed the all processes of AVF care and remained patent for dialysis. Future efforts to increase the prevalence of AVFs in older hemodialysis patients should focus on early

placement in the proper candidates. Disparities in practice patterns needed to be addressed to improve AVF care outcomes.

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Table 1. Baseline characteristics of three study cohorts of elderly patients who initiated hemodialysis with a central venous catheter.

	Cohort 1	Cohort 2	Cohort 3
Total cohort	**43,851**	**14,892**	**7,528**
Demographics			
Age at dialysis initiation (yrs)(mean±SD)	77.1±6.7	76.7±6.5	76.6±6.4
67-<75	17,370(39.6)	6,196(41.6)	3,158(42)
75-<85	19,536(44.6)	6,641(44.6)	3,373(44.8)
≥85	6,945(15.8)	2,055(13.8)	997(13.2)
Gender			
Male	22,990(52.4)	8,115(54.5)	4,524(60.1)
Female	20,861(47.6)	6,777(45.5)	3,004(39.9)
Race			
White	33,067(75.4)	11,322(76)	5,798(77)
Black	8,747(20)	2,755(18.5)	1,270(16.9)
Other/unknown	20,37(4.7)	815(5.5)	460(6.1)
Region			
Northeast	7,781(17.7)	2,386(16)	1,195(15.9)
Midwest	11,017(25.1)	3,941(26.5)	2,021(26.9)
South	16,800(38.3)	5,890(39.6)	2,872(38.2)
West	7,979(18.2)	2,610(17.5)	1,414(18.8)
Comorbid conditions			
Primary cause of renal failure			
Hypertension/Large vessel disease	15,454(35.2)	5,453(36.6)	2,762(36.7)
Diabetes	17,024(38.8)	6,236(41.9)	3,092(41.1)
Glomerulonephritis	1,351(3.1)	527(3.5)	309(4.1)
Other	10,022(22.9)	2,676(18)	1,365(18.1)
Diabetes	28,646(65.3)	10,235(68.7)	5,035(66.9)
Hypertension	32,564(74.3)	12,839(86.2)	6,441(85.6)
Coronary artery disease	27,839(63.5)	9,533(64)	4,703(62.5)
Myocardial infarction	11,347(25.9)	3,665(24.6)	1,722(22.9)
Atherosclerosis	26,750(61)	9,227(62)	4,552(60.5)
Coronary revascularization	2,576(5.9)	854(5.7)	425(5.7)
Congestive heart failure	30,619(69.8)	10,463(70.3)	5,101(67.8)
Peripheral vascular disease	23,052(52.6)	7,848(52.7)	3,835(50.9)
Cerebrovascular disease	13,594(31)	4,670(31.4)	2,297(30.5)
Stroke	5,865(13.4)	1,785(12)	827(11)
Chronic obstructive pulmonary disease	16,822(38.4)	5,757(38.7)	2,754(36.6)
Cancer	8,951(20.4)	2,968(19.9)	1,518(20.2)
Depression	7,633(17.4)	2,437(16.4)	1,136(15.1)
Dementia	3,627(8.3)	995(6.7)	463(6.2)
Functional status			
Amputation	673(1.5)	191(1.3)	98(1.3)
Inability to ambulate	5,578(12.7)	1,239(8.3)	500(6.6)
Inability to transfer	3,342(7.6)	616(4.1)	238(3.2)
Needs assistance with daily activities	9,569(21.8)	2,552(17.1)	1,134(15.1)
Institutionalized	7,803(17.8)	1,835(12.3)	759(10.1)
Lab values			
Body mass index (kg/m^2)(mean±SD)	28.2±7.3	28.5±7.3	28.2±7
Hemoglobin (g/dl, mean ± SD)	10±13.8	10±13.6	10.2±18.9
Serum albumin (g/dl, mean ± SD)	3.1±3.7	3.2±5.5	3.3±6.4
GFR (ml/min/1.73 m^2, mean ± SD)	13.5±5.8	13.1±5.6	12.8±5.5

Care patterns			
Nephrology care			
No care	22,806(52)	6,799(45.7)	3,385(45)
0-6 months	6,318(14.4)	2,311(15.5)	1,188(15.8)
6-12 months	6,355(14.5)	2,393(16.1)	1,233(16.4)
12 months	8,372(19.1)	3,389(22.8)	1,722(22.9)
Facility type			
Hospital-based	4,045(9.3)	1,320(8.9)	734(9.8)
Freestanding	39,701(90.8)	13,532(91.1)	6,776(90.2)
Profit status			
For-profit	36,430(83.3)	12,460(83.9)	6,162(82.1)
Non-profit	6,913(15.8)	2,316(15.6)	1,311(17.5)
Unknown	403(0.9)	76(0.5)	37(0.5)

GFR: Glomerular filtration rate. Missing values in cohort 1, 2, and 3 respectively: BMI (0.8 %, 0.6%, and 0.6%); hemoglobin (8.8%, 8.5%, and 8.4%); albumin (27%, 26.3%, and 25.9%); GFR (4.6%, 3.2%, and 2.8%); facility type (0.2%, 0.3%, 0.2%); profit status (0.2%, 0.3%, 0.2%); and region(0.6%, 0.4%, 0.4%).

Table 2. Number and incident rate of pre-maturation interventions in patients with maturated fistulas and post-maturation in patients who maintained fistula secondary patency.

End point	N	Mean	STD	Median	IQR	Min	Max
Pre-maturation interventions	10,260	1.4	2.2	1	0-2	0	42
Incident rate of pre-maturation interventions (per patient per month)	10,260	0.2	0.3	0.1	0-0.3	0	8.4
Post-maturation revisions	3,352	3.1	3.4	2	1-5	0	27
Incident rate of post-maturation revisions (per patient per month)	3,352	0.1	0.1	0.1	0-0.2	0	1.1

Figure 1. Development of the study cohorts.

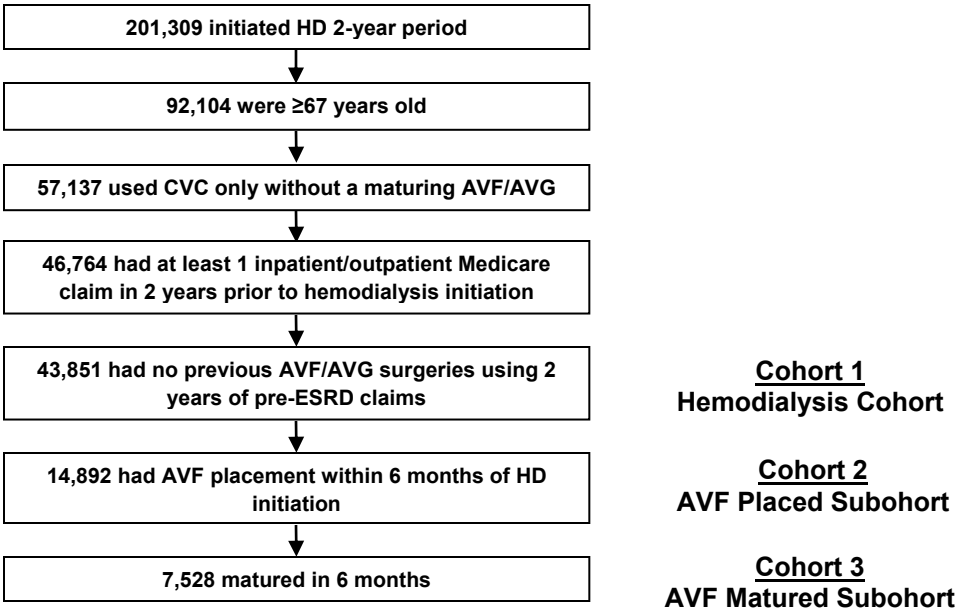

201,309 initiated HD 2-year period
92,104 were ≥67 years old
57,137 used CVC only without a maturing AVF/AVG
46,764 had at least 1 inpatient/outpatient Medicare claim in 2 years prior to hemodialysis initiation
43,851 had no previous AVF/AVG surgeries using 2 years of pre-ESRD claims
Cohort 1
Hemodialysis Cohort
14,892 had AVF placement within 6 months of HD initiation
Cohort 2
AVF Placed Subohort
7,528 matured in 6 months
Cohort 3
AVF Matured Subohort

Figure 2. Care continuum of arteriovenous fistula (AVF) among older adults undergoing hemodialysis including AVF placement within 3 years of dialysis initiation, AVF maturation within 2 years of replacement, and AVF maintained secondary patency within 2 years of maturation.

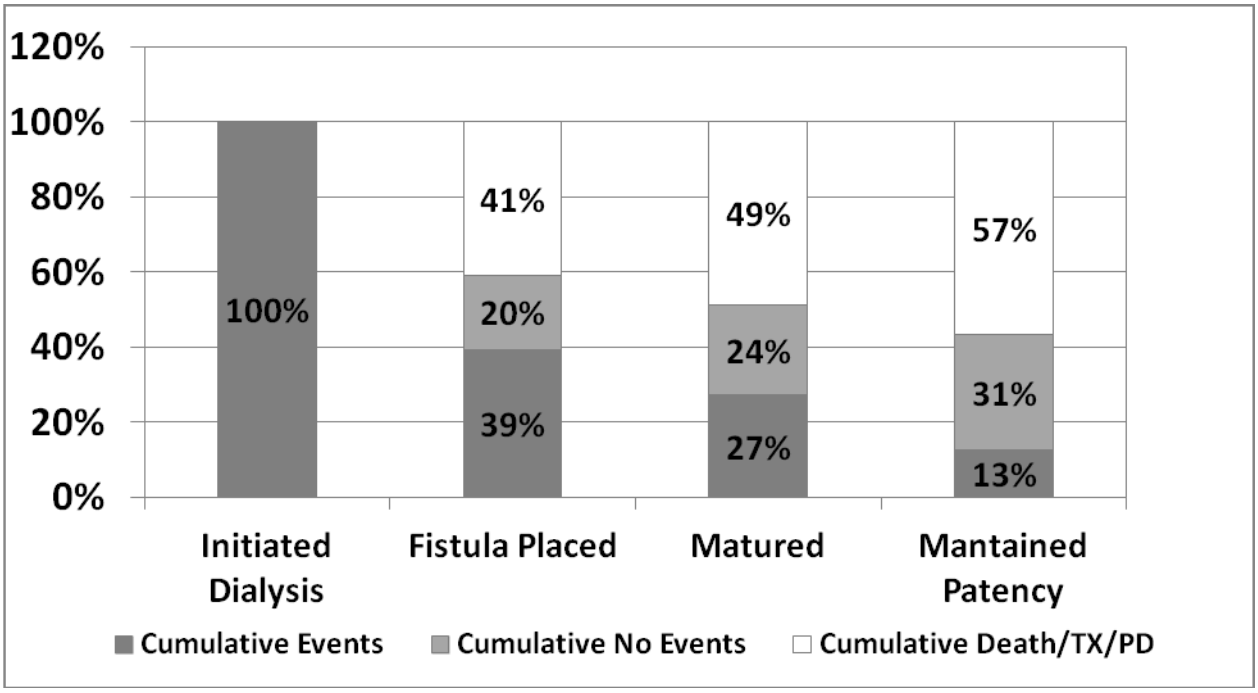
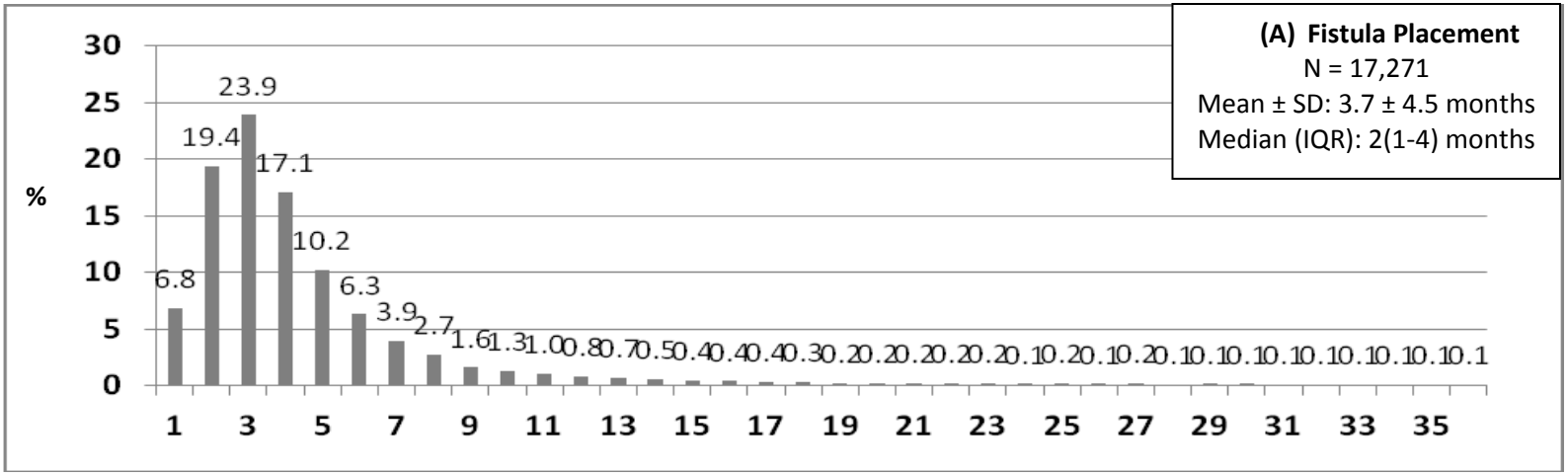
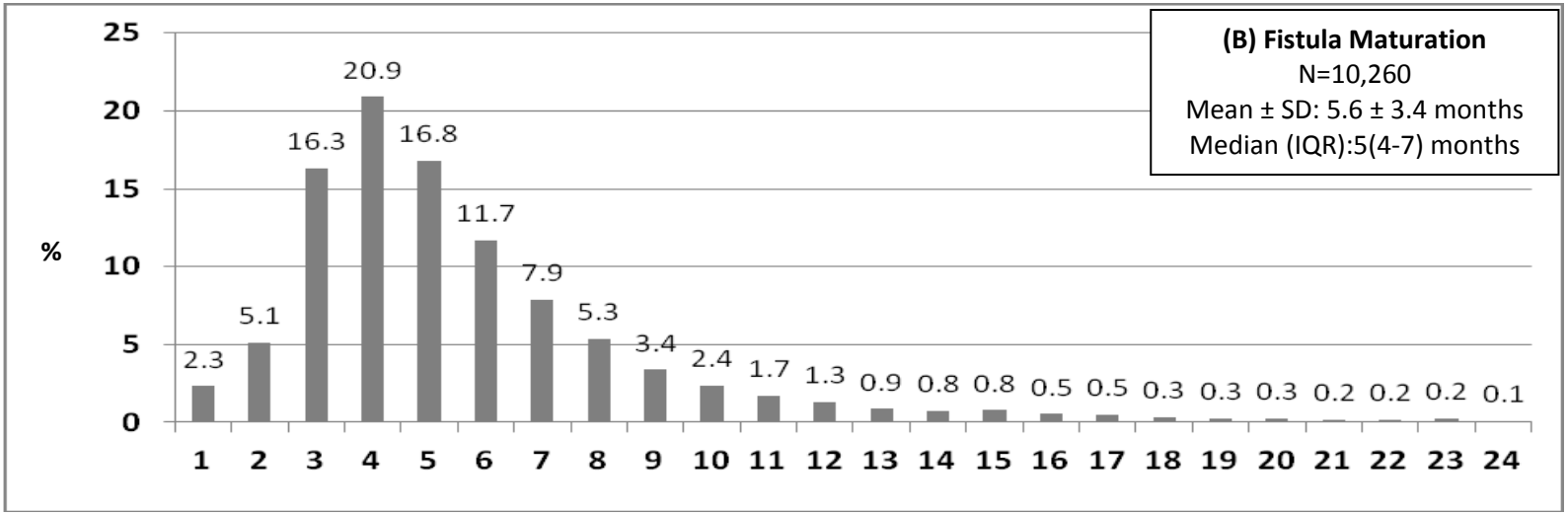

120%
100%
80%
60%
40%
20%
0%
100%
41%
20%
39%
49%
24%
27%
57%
31%
13%
Initiated Dialysis
Fistula Placed
Matured
Mantained Patency
Cumulative Events
Cumulative No Events
Cumulative Death/TX/PD

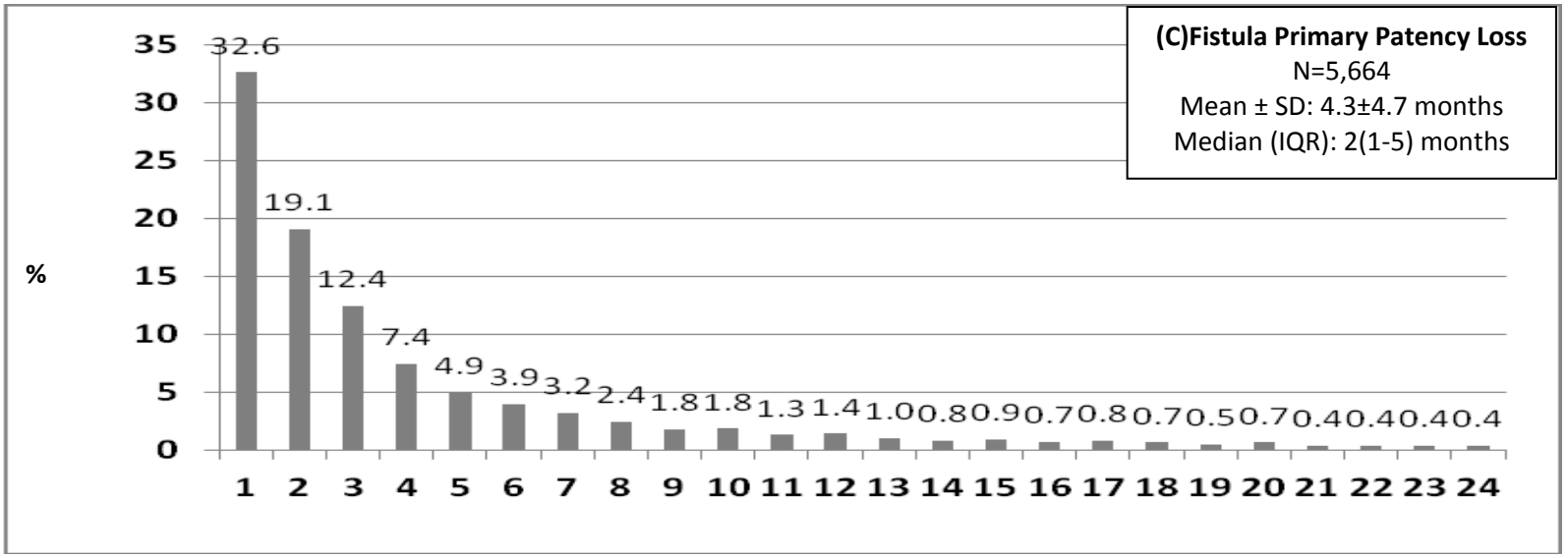
Figure 3. Monthly distribution of arteriovenous fistula (AVF) outcomes in older U.S. hemodialysis recipients. (A) AVF placement within 3 years of dialysis initiation; (B) AVF maturation within 2 years of replacement; (C) AVF primary patency loss within 2 years of maturation; (D) AVF abandonment within 2 years of maturation.



Within Month(s) of Dialysis Initiation



Within Month(s) of Fistula Placement


(C)Fistula Primary Patency Loss
N=5,664
Mean ± SD: 4.3±4.7 months
Median (IQR): 2(1-5) months
%
35
30
25
20
15
10
5
0
32.6
19.1
12.4
7.4
4.9
3.9
3.2
2.4
1.8
1.8
1.3
1.4
1.0
0.8
0.9
0.7
0.8
0.7
0.5
0.7
0.4
0.4
0.4
0.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Within Month(s) of Fistula Maturation

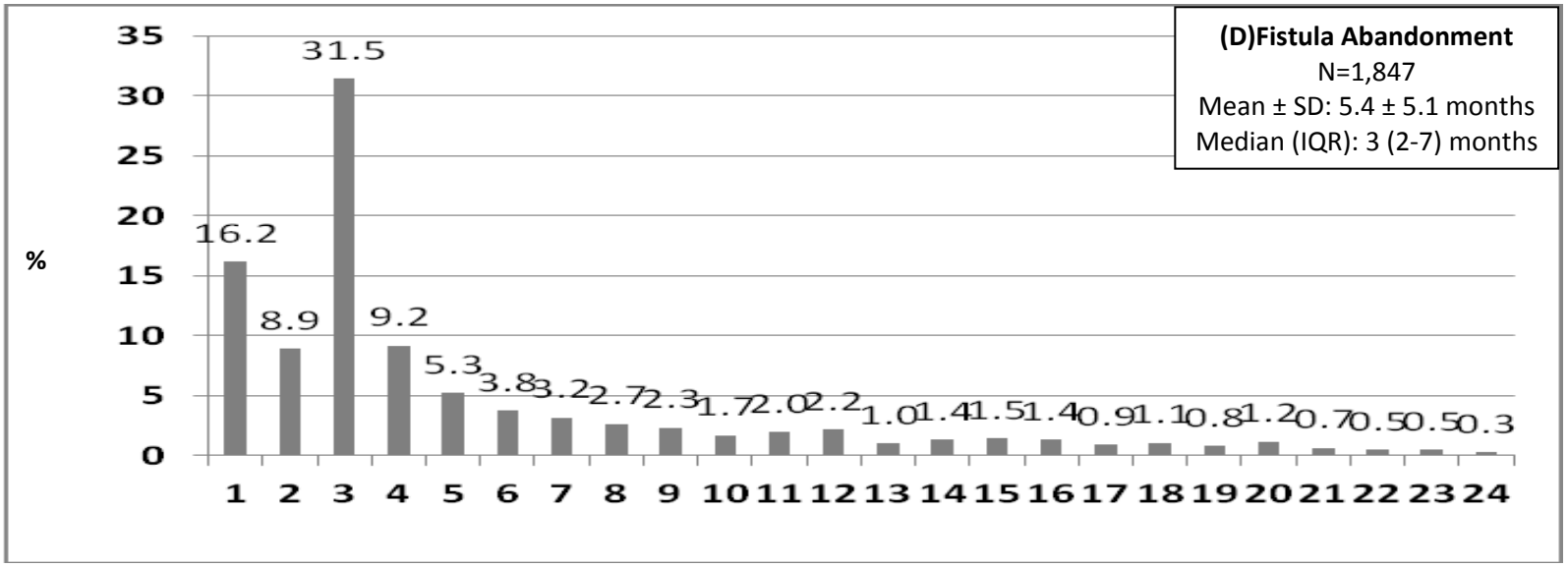
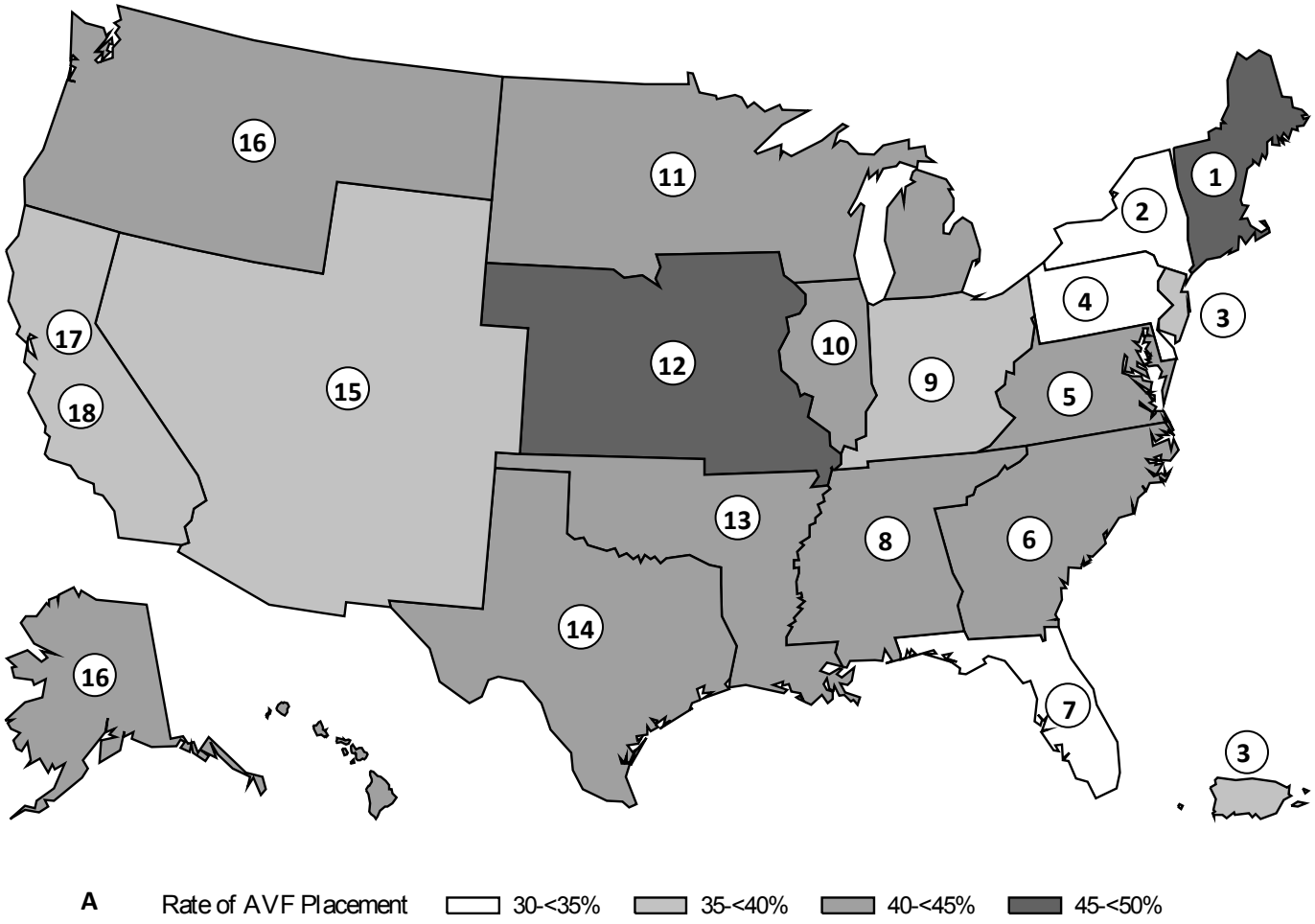
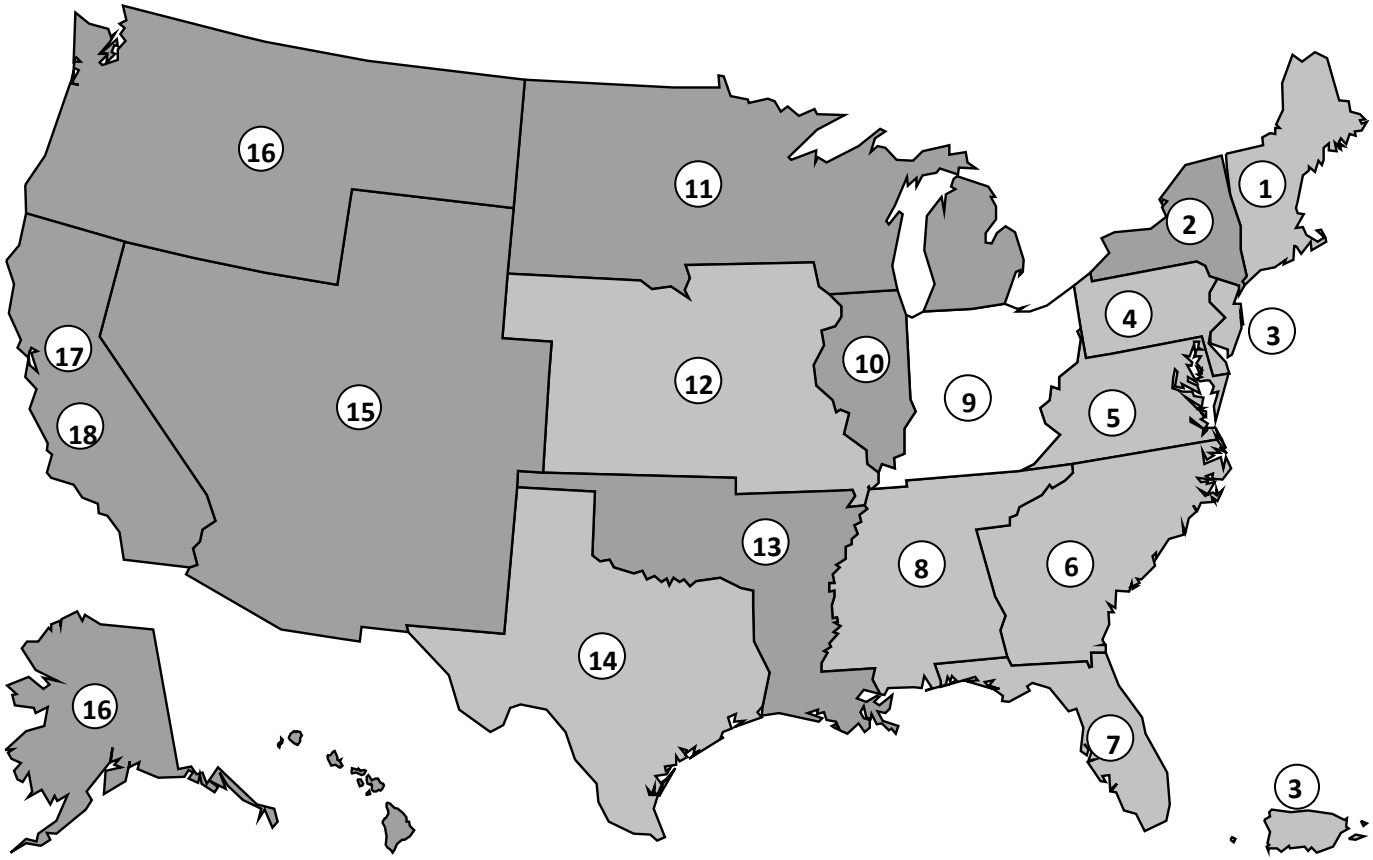
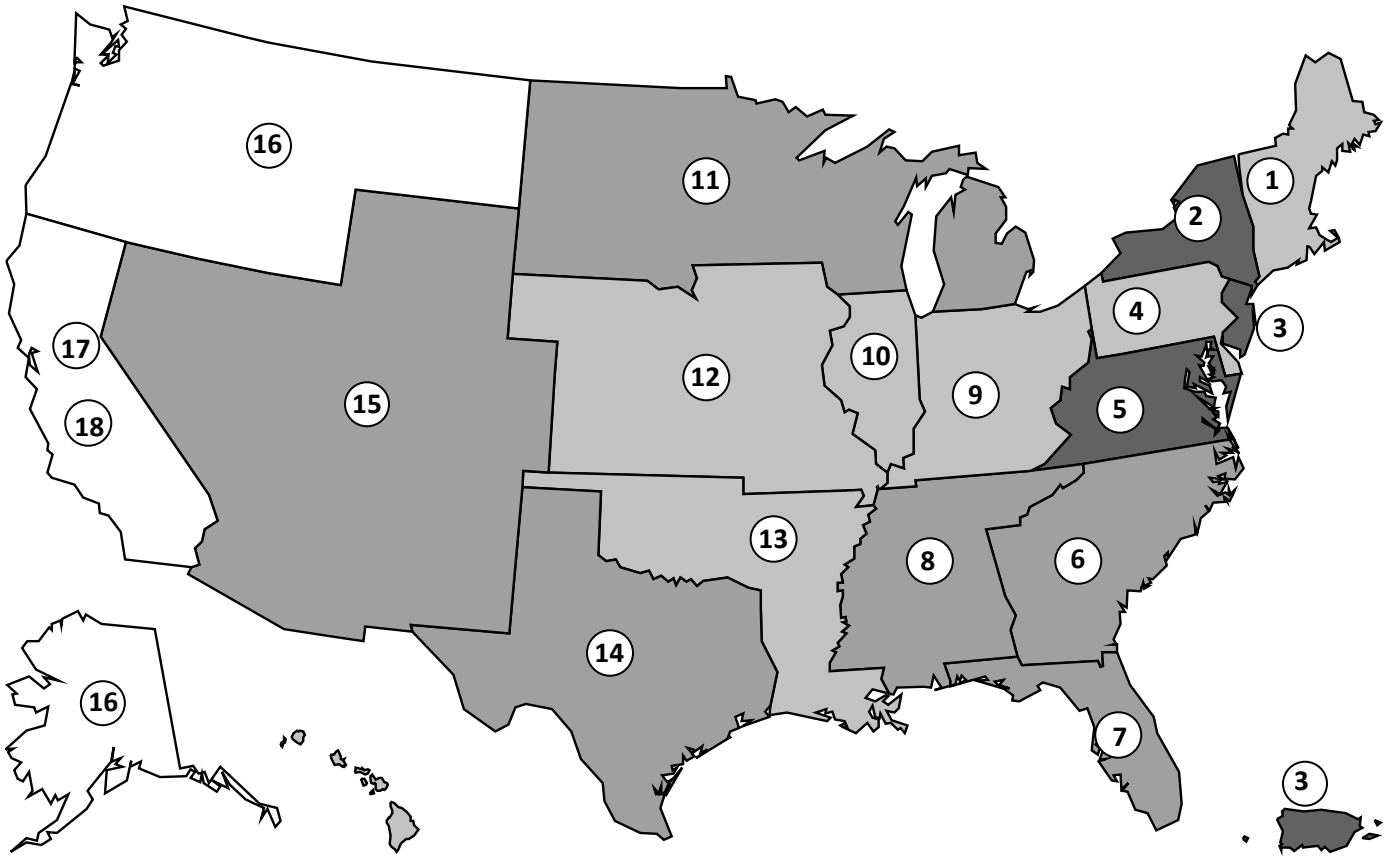

(D)Fistula Abandonment
N=1,847
Mean ± SD: 5.4 ± 5.1 months
Median (IQR): 3 (2-7) months
%
35
30
25
20
15
10
5
0
16.2
8.9
31.5
9.2
5.3
3.8
3.2
2.7
2.3
1.7
2.0
2.2
1.0
1.4
1.5
1.4
0.9
1.1
0.8
1.2
0.7
0.5
0.5
0.3
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Within Month(s) of Fistula Maturation

Figure 4. Distribution of arteriovenous fistula (AVF) outcomes by geographic region in older U.S. hemodialysis recipients. (A) AVF placement within 3 years of dialysis initiation; (B) AVF maturation within 2 years of replacement; (C) AVF primary patency loss within 2 years of maturation; (D) AVF abandonment within 2 years of maturation.


16
11
1
2
4
3
17
12
10
9
5
18
15
13
8
6
14
16
7
3
A
Rate of AVF Placement
30-<35%
35-<40%
40-<45%
45-<50%


16
11
1
2
4
3
17
10
12
9
15
5
18
13
8
6
14
16
7
3
B
Rate of AVF Maturation
60-<65%
65-<70%
70-<75%


16
11
1
2
4
3
17
12
10
9
5
15
18
13
8
6
14
16
7
3
C Rate of AVF Primary Patency Loss
65-<70%
70-<75%
75-<80%
80-<85%

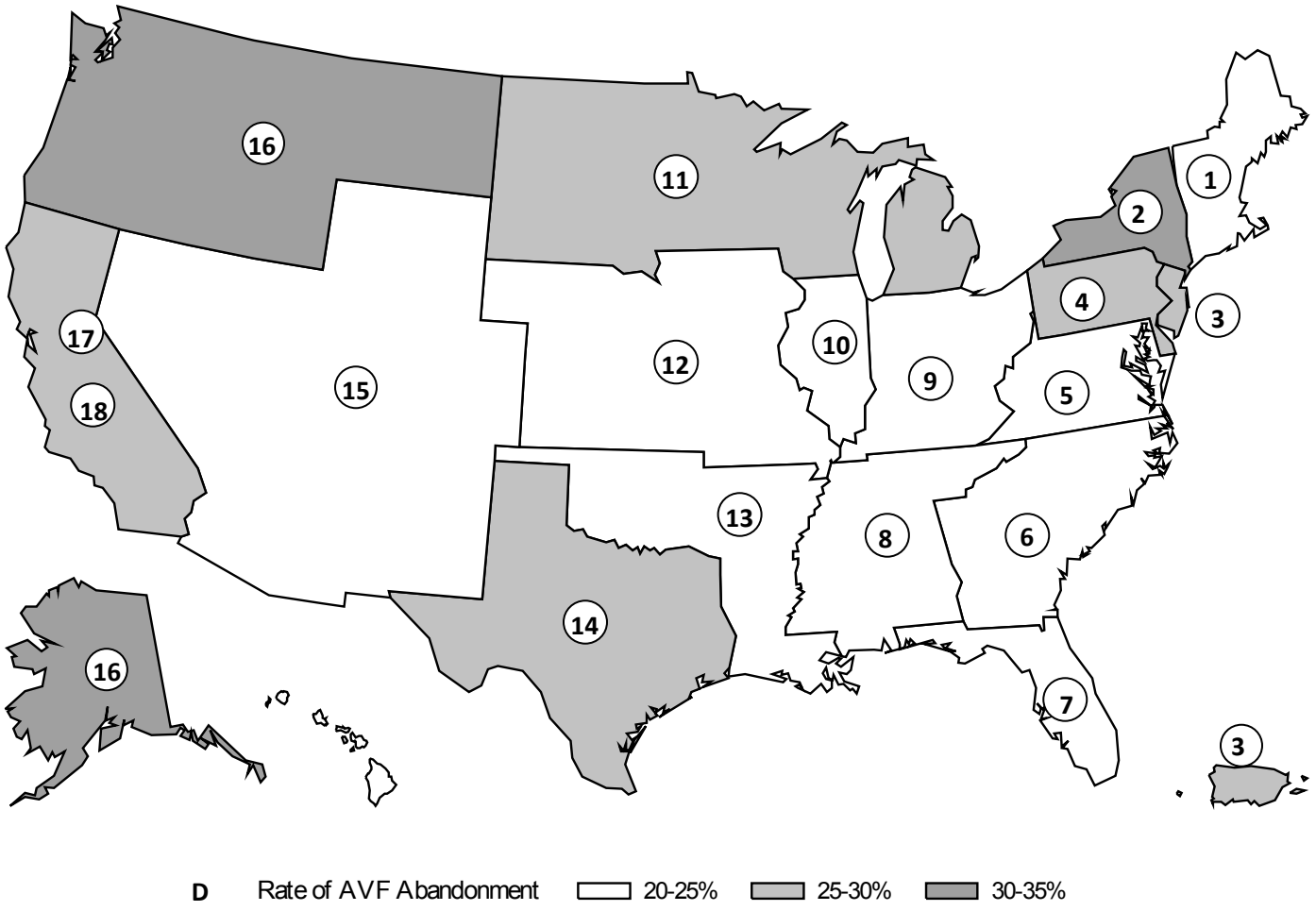
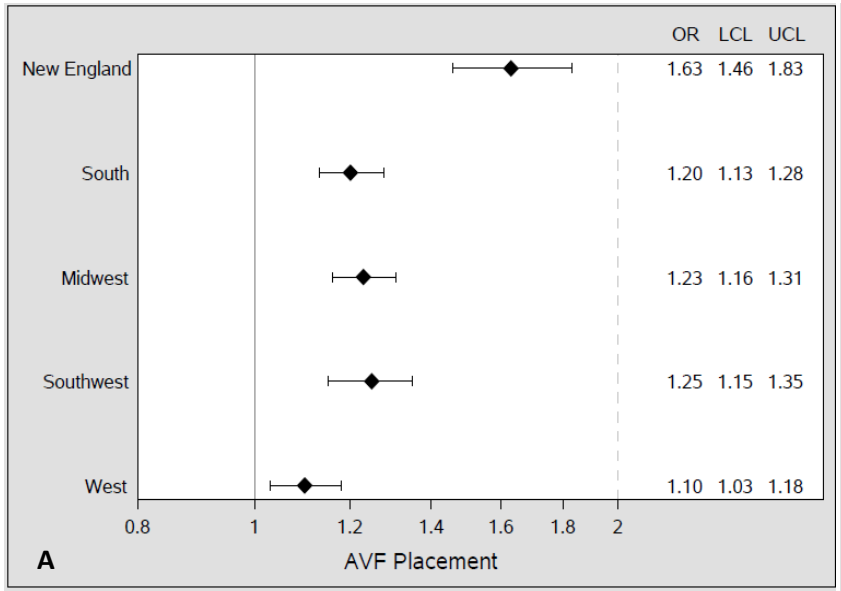
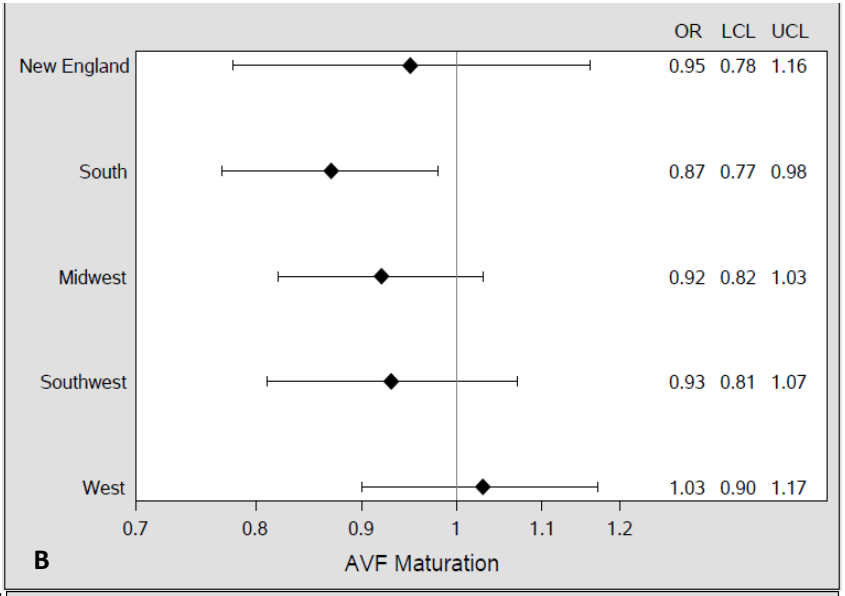
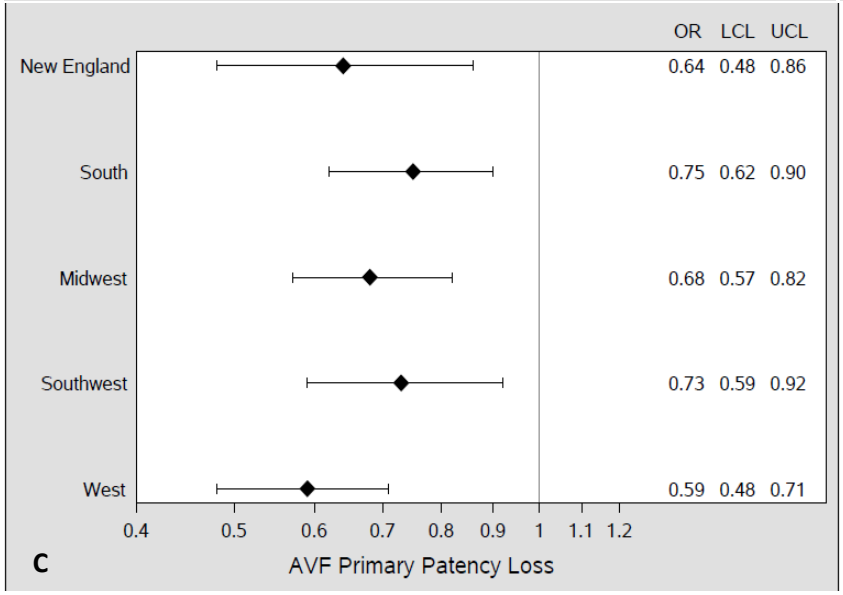

16
11
1
2
4
3
17
15
12
10
9
5
18
13
8
6
14
16
7
3
D
Rate of AVF Abandonment
20-25%
25-30%
30-35%

Figure 5. Adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) for arteriovenous fistula (AVF) outcomes by geographic region in older U.S. hemodialysis recipients. (A) AVF placement within 3 years of dialysis initiation; (B) AVF maturation within 2 years of replacement; (C) AVF primary patency loss within 2 years of maturation; (D) AVF abandonment within 2 years of maturation. The Mid-Atlantic region is the reference group.


OR LCL UCL
New England 1.63 1.46 1.83
South 1.20 1.13 1.28
Midwest 1.23 1.16 1.31
Southwest 1.25 1.15 1.35
West 1.10 1.03 1.18
0.8 1 1.2 1.4 1.6 1.8 2
A
AVF Placement


OR LCL UCL
New England 0.95 0.78 1.16
South 0.87 0.77 0.98
Midwest 0.92 0.82 1.03
Southwest 0.93 0.81 1.07
West 1.03 0.90 1.17
0.7 0.8 0.9 1 1.1 1.2
B
AVF Maturation


OR LCL UCL
New England 0.64 0.48 0.86
South 0.75 0.62 0.90
Midwest 0.68 0.57 0.82
Southwest 0.73 0.59 0.92
West 0.59 0.48 0.71
0.4 0.5 0.6 0.7 0.8 0.9 1 1.1 1.2
C
AVF Primary Patency Loss

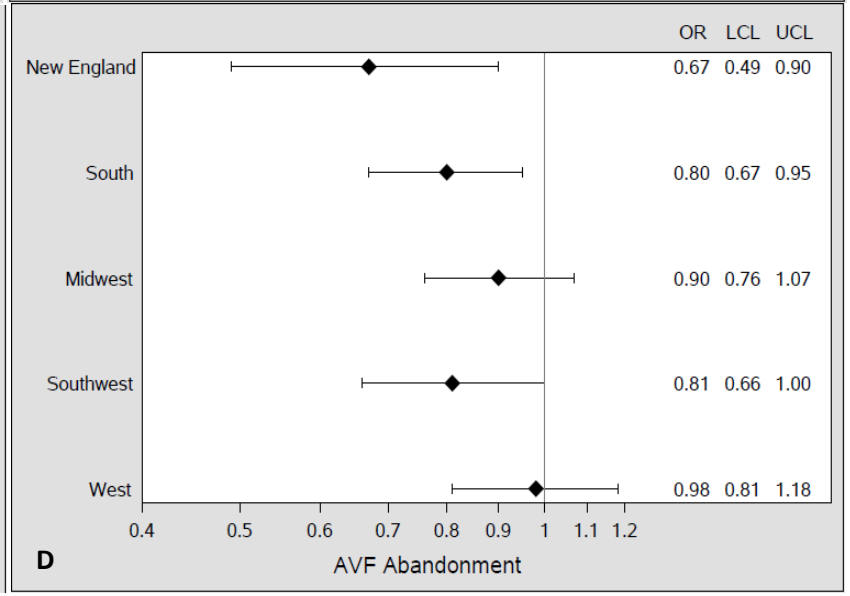

OR LCL UCL
New England 0.67 0.49 0.90
South 0.80 0.67 0.95
Midwest 0.90 0.76 1.07
Southwest 0.81 0.66 1.00
West 0.98 0.81 1.18
0.4 0.5 0.6 0.7 0.8 0.9 1 1.1 1.2
D
AVF Abandonment

Table S1. Codes of surgical and endovascular procedures associated with hemodialysis arterovenous fistula management.

Type of intervention	Codes
Open surgical procedures	**CPT-4 Codes**
Revision, open, arteriovenous fistula; with thrombectomy, autogenous or nonautogenous dialysis graft	36833
Revision of fistula or graft	36832
Fistula elevation or superficialization	36832
Ligation of accessory veins	36832
Open surgical procedures for treatment of steal syndrome	36832
Open repair of pseudoaneurysm	36832
Banding fistula or graft	36832
Open thrombectomy, arteriovenous fistula without revision, autogenous or nonautogenous dialysis graft	36831
Endovascular interventions	**CPT-4 Codes**
Angiogram with venous angioplasty	36147, 35476, 75978
Angiogram with arterial angioplasty	36147, 35475, 75962
Angiogram with venous angioplasty and stent	36147, 37205, 37206 (rarely +37239)
Angiography, arteriovenous shunt (e.g., dialysis patient fistula / graft)	75791 (must be present with other interventions)
Percutaneous thrombectomy	36870 (also 36147, 36148)
Percutaneous thrombectomy with venous angioplasty	36870, 36147, 36148, 35476, 75978
Percutaneous thrombectomy with arterial angioplasty	36870, 36147, 36148, 35475, 75962
Percutaneous thrombectomy with venous angioplasty and stent	36870, 36147, 36148, 37205, 37206 (rarely +37239)
Inpatient procedures	**ICD-9 Codes**
Compression of vein	459.2
Mechanical complications of vascular device, implant and graft	996.1
Other complication of vascular device, implant and graft	996.7

Table S2. Frequency and incident rate of pre-maturation interventions in patients with matured fistula. Interventions in the same month of maturation were analyzed as pre-maturation intervention.

	N	Mean	STD	Median	IQR	Min	Max
Pre-maturation interventions	10,260	1.7	2.3	1	0-3	0	53
Incident rate of pre-maturation interventions (per patient per month)	10,260	0.3	0.4	0.2	0-0.4	0	10.6

CHAPTER THREE

AGE AND ARTERIOVENOUS FISTULA PLACEMENT, MATURATION, AND PATENCY LOSS IN OLDER HEMODIALYSIS ADULTS

ABSTRACT

Rational & Objective: Choosing the optimal vascular access for older adults on hemodialysis is challenging. Precisely estimation of the effect of age on arteriovenous fistula (AVF) outcomes provides valuable information for clinical decision making. Our study aimed to determine the association of age with AVF placement, maturation, and primary and secondary patency loss in the U.S. older hemodialysis recipients.

Study Design: Retrospective cohort study

Setting & Participants: Three national cohorts of incident hemodialysis patients aged 67 years and older who initiated dialysis (43,851), had an AVF placed (14,892), or had the placed AVF matured (7,528) assembled from the United States Renal Data System

Exposure: Age at dialysis initiation

Outcomes: AVF placement, maturation, primary and secondary patency loss

Analytical Approach: Cause-specific and subdistribution proportional hazards models were used to examine the association of age and AVF outcomes with kidney transplantation, peritoneal dialysis, and death treated as competing events. Restricted cubic splines were used to identify cut-off values for age categorization. We compared crude and inverse probability weighted cumulative incidence function curves by Gray's test.

Results: Patients ≥77 years old had significantly lower probabilities of AVF placement (adjusted cHR 0.96, 95% CI 0.92-0.99; adjusted sHR 0.92, 95% CI 0.89-0.95; Gray's test p<.0001) and maturation (adjusted cHR 0.95, 95% CI 0.91-0.99; adjusted sHR 0.93, 95% CI 0.90-0.97; p<.0001) as compared to those 67-<77. However, age is not associated with AVF primary patency loss (adjusted cHR 1.05, 95% CI 1.00-1.11; adjusted sHR 1.04, 95% CI 0.99-1.09;

p=0.091) or secondary patency loss (adjusted cHR 1.05, 95% CI 0.95-1.15; adjusted sHR 1.03, 95% CI 0.94-1.13; *p*=0.613).

Limitations: Vascular access ascertainment

Conclusion: The likelihood of AVF maturation should be the most important consideration for vascular access planning in older hemodialysis recipients. AVF might not the best vascular access option for patients approaching eighty years old.

INTRODUCTION

Older adults are the fastest growing segment of the prevalent population with end-stage kidney disease (ESKD). In 2016, 47.4% of U.S. patients undergoing hemodialysis therapy were 65 years or older[1]as compared to 44.7% in 2010.[2] Older dialysis recipients present a special challenge to ESKD care community because of their heavy comorbid burdens, limited functional and cognitive ability, and shorten life expectancy.[3,4]

Current clinical guidelines recommend the arteriovenous fistula (AVF) as the optimal type of vascular access for hemodialysis.[5] This recommendation was based on observational data that AVF, once functional, are less prone to infection and are associated with reduced all-cause mortality as compared to arteriovenous graft (AVG) and central venous catheters (CVC).[6,7] In older dialysis recipients, matured AVF achieves longer patency and requires less interventional procedures to maintain functionality as compared to AVG.[8] In the short-term, however, AVF is less likely to mature and needs higher frequency of interventions to achieve maturation as compared to AVG.[8] This leads to prolonged CVC use, which is related to substantially elevated rates of infection [9,10] and increased all-cause mortality.[11,12] Older patients, especially those who are likely to have short life expectancy and worse AVF outcomes, face the dilemma whether they should have an AVF or AVG placed as the primary vascular access. So far there is no clear clinical recommendation for AVF placement using age as a criterion and clinical decision is left to vascular surgeon's individual decision.

In general, evidence on the association of age and AVF outcomes was scarce in the literature. Definitions of "elderly" in these studies are often inconsistent and the results of AVF outcomes are conflicting. This study aims to examine the association of age with AVF outcomes including AVF placement, maturation, and primary and secondary patency loss in the U.S. older

adults undergoing hemodialysis. Precisely estimation of the effect of age on AVF outcomes provides valuable information to assist individual vascular access plan development.

METHODS

Data Source and Study Population

Our primary data source was derived from the 2010-2015 United States Renal Data System (USRDS) standard analytic files (SAFs). **Figure 1** demonstrated development of our study cohorts. Cohort 1, the hemodialysis cohort, included 43,851 incident hemodialysis recipients aged 67 years and older who initiated dialysis through a CVC between 7/1/2010 and 6/30/2012. To ensure that the CVC was the only vascular access present at the start of dialysis therapy, patients were excluded if they: (1) were using an AVF or AVG or had an AVF or AVG placed but were awaiting maturation at dialysis initiation, as reported in the Medical Evidence Form; (2) underwent AVF or AVG surgery in the 2-year pre-end stage renal disease (ESRD) period, as assessed by Current Procedural Terminology-4 (CPT-4) procedure codes of 36818, 36819, 36820, 36821, and 36825 for AVF and 36800, 36810, and 36830 for AVG. From the hemodialysis cohort (cohort 1), we further identified two subcohorts. Cohort 2, the AVF placed cohort, included 14,569 patients who had an AVF placement within 6 months after dialysis initiation. Cohort 3, the AVF matured cohort, included 7,301 patients whose AVFs matured within 6 months after placement.

Study Outcomes

The primary outcomes of this study were AVF placement (cohort 1), AVF maturation (cohort 2), and AVF primary and secondary patency loss (cohort 3). We identified AVF

placement from the physician/supplier claims and institutional claims files, which record the exact date of AVF construction, by using the same CPT-4 codes as listed above. Different from AVF placement, AVF maturation and patency loss were ascertained by month. AVF maturation was determined by using the first vascular access modifier code 'V7' reported from the institutional details claims file or the first AVF used with two needles reported from the Crownweb clinical file. We defined AVF primary patency loss as the first revision procedure after maturation. Codes used to identify intervention procedures were listed in **Table S1**. We defined AVF secondary patency loss (abandonment) as 3 consecutive months of CVC use or a new vascular access placement. Cohort 1 was followed for 3 years from dialysis initiation. Cohort 2 was followed for 2 years from AVF placement. Cohort 3 was followed for 2 years from AVF maturation.

Competing Events

A competing event in this study was defined as kidney transplantation, peritoneal dialysis transfer, or death, whichever occurred first in the follow-up period. Competing events were determined by using the transplant file, dialysis institutional claims file, and death file, respectively.

Covariates of Interest

Age at dialysis initiation was study exposure. We extracted patient demographics, residential region, BMI, functional status, lab values, primary cause of renal failure, and pre-dialysis nephrology care from the Medical Evidence Form. In addition, 2-year pre-ESRD claims files were used to identify major comorbid conditions. ESRD network number, facility profit

status, and hospital association were ascertained from the facility file and merged to patient-level data by using facility provider ID.

Statistical Analysis

We presented summary statistics as frequency and percentages for categorical data and means ± SDs for continuous variables by patient's age at dialysis initiation. In each cohort, we classified patients into three mutually exclusive groups according to whether they experienced the outcome of interest (AVF placement, maturation, primary patency loss, and abandonment) or a competing event: (1) patient experienced the outcome of interest; (2) patient had a competing event; and (3) patient did not experience the outcome of interest or a competing event. To properly categorize the continuous age into groups, we tested the assumption of a linear relationship between age and log hazard ratios of AVF outcomes by using restricted cubic spline function.[13,14] Any breakpoint in linearity or change in slope of cubic splines was viewed as a change in effect of age on AVF outcomes. We tested different knot numbers and locations and selected spline functions with 3 knots at 10th, 50th, and 90th percentile. When evidence of a non-linear relationship was found, we identified the break points and used them to categorize age. We used the cause-specific and subdistribution proportional hazards models to explore the possible association between age group and AVF outcomes. Two sets of cause-specific hazard ratios (cHRs) and subdistribution hazard ratios (sHRs), the first for AVF outcomes and the second for competing events, were reported. [15] Specifically, the cHRs of AVF outcomes were calculated with competing events censored and the cHRs of competing events were obtained with AVF outcomes censored. The proportional hazards assumption was checked by examining age and time interaction and by plotting log of negative log of estimated survival function versus

log of time in the cause-specific models. When the proportional hazards assumption is satisfied, the graph should show parallel lines and the statistical test of age and time interaction should be insignificant. To accommodate any violation of proportional hazards assumption, we also generated the non-parametric inverse probability weighted cumulative incidence function (CIF) curves[16] and implemented Gray's test for equivalence of CIF to compare weighted cumulative incidence by age groups. Inverse probability weights are the inverse of propensity scores, which are the estimated probabilities of treatment assignment conditioned on covariates. Different from the log-rank test for cause-specific hazards, Gray's test accesses the absolute difference in incidence of events between age groups.[17] Statistical analyses were performed using SAS (version 9.4; SAS institute, Cary, NC). All statistical tests were two-sided, and a p-value < 0.05 considered statistically significant. Institutional review board approval for an exempt review was obtained from Bloomberg School of Public Health at Johns Hopkins University. We used the STROBE guidelines to improve the reporting of our observational research study.

RESULTS

Age Categorization

Figure S1 indicated that only effect of age at dialysis initiation on the log hazard ratios of AVF placement was not linear ($p<.0001$). Age 76 or 77 corresponded to a break point in the splines. Effect of age between 67-<77 was homogenous, but after 77, hazard ratios of AVF placement decreased rapidly with age. Accordingly, we assumed effect of age on hazard ratios of AVF placement after 77 was same and chose age of 77 as a convenient cut-off value to classify patients into two groups.

Baseline Characteristics

Table 1 listed patient demographics, comorbid conditions, functional status, lab values, and care patterns by two categories of age at dialysis initation. Patients 67-<77 years old were more likely to be male (53.1% vs. 51.8%) and Black (23.2% vs. 16.7%) as compared to those ≥77. Not surprisingly, patients aged ≥77 years old carried higher comorbid burdens and had worse functional status, as compared to those 67-<77. Nutrition status (hemoglobin and serum albumin values) and practice patterns were similar between two age groups.

Age and AVF Placement

Of 43,851 patients who initiated dialysis with a CVC in the hemodialysis cohort (cohort 1), 39.4% of them had an AVF placed within 3 years of dialysis initiation, 40.8% experienced a competing event, and 19.8% kept dialyzing with a CVC or had other forms of vascular access placed (**Table 2**). As compared to patients 67-<77, those ≥77 years old had significantly lower probability to have an AVF placed (unadjusted cHR 0.93, 95% CI 0.90-0.96; adjusted cHR 0.96, 95% CI 0.92-0.99; unadjusted sHR 0.86, 95% CI 0.84-0.89; adjusted sHR 0.92, 95% CI 0.89-0.95) but higher probability of experiencing a competing event (unadjusted cHR 1.36, 95% CI 1.32-1.40; adjusted cHR 1.19, 95% CI 1.15-1.24; unadjusted sHR 1.36, 95% CI 1.32-1.40; adjusted sHR 1.20, 95% CI 1.16-1.25) (**Table 3A** and **3B**). Results of Gray's test for equality of weighted CIF also confirmed age was statistically significantly associated with AVF placement (p<.0001) (**Figure 2**).

Age and AVF Maturation

In the AVF placed cohort (cohort 2), 68.9% of 14,892 patients achieved AVF maturation, 20.3% experienced a competing event, and 10.8% maintained on dialysis without a matured AVF 2 years after AVF placement (**Table 2**). Proportional hazards regressions showed AVFs placed in patients ≥77 years old were less likely to mature as compared to those in patients 67-<77 (unadjusted cHR 0.95, 95% CI 0.91-0.99; adjusted cHR 0.95, 95% CI 0.91-0.99; unadjusted sHR 0.91, 95% CI 0.87-0.94; adjusted sHR 0.93, 95% CI 0.90-0.97) (**Table 3A and 3B**). They were more likely to have a competing event (unadjusted cHR 1.33, 95% CI 1.24-1.43; adjusted cHR 1.17, 95% CI 1.08-1.26; unadjusted sHR 1.35, 95% CI 1.25-1.45; adjusted sHR 1.19, 95% CI 1.10-1.28) (**Table 3A and 3B**). Gray's test also demonstrated the association of age and AVF maturation was statistically significant (p<.0001) (**Figure 2).**

Age and AVF Primary Patency Loss

Among 7,528 patients in the AVF matured cohort (cohort 3), 75.2% of them experienced AVF primary patency loss, and 13.9% had a competing event (**Table 2**). Cause-specific hazards analyses showed age was significantly associated with AVF primary patency loss (unadjusted cHR 1.05, 95% CI 1.00-1.11; adjusted cHR 1.05, 95% CI 1.00-1.11) (**Table 3A**). However, both the subdistribution hazards regressions and Gray's test revealed difference in AVF primary patency loss was not statistically significant by age groups (unadjusted sHR 1.03, 95% CI 0.98-1.08; adjusted sHR 1.04, 95% CI 0.99-1.09; p=0.091) (**Table 3B and Figure 2**). Age patients ≥77 years old were more likely to have a competing event as compared to those 67-<77 (unadjusted cHR 1.44, 95% CI 1.25-1.65; adjusted cHR 1.12, 95% CI 0.99-1.27; unadjusted sHR 1.09, 95% CI 0.97-1.23; adjusted sHR 1.04, 95% CI 0.92-1.18) (**Table 3A and 3B**).

Age and AVF Abandonment

Overall 25.2% of matured AVFs in the AVF matured cohort (cohort 3) were abandoned. Approximately half (46.4%) of patients with matured AVFs continued to use their AVFs for dialysis and 28.4% of patients experienced a competing event 2 years after AVF maturation (**Table 2**). Age was not associated with an increased risk for AVF abandonment (unadjusted cHR 1.07, 95% CI 0.98-1.17; adjusted cHR 1.05, 95% CI 0.95-1.15; unadjusted sHR 1.04, 95% CI 0.95-1.14; adjusted sHR 1.03, 95% CI 0.94-1.13; p=0.613) but patients ≥77 years old had higher likelihood of experiencing a competing event (unadjusted cHR 1.48, 95% CI 1.35-1.61; adjusted cHR 1.33, 95% CI 1.22-1.46; unadjusted sHR 1.43, 95% CI 1.31-1.56; adjusted sHR 1.30, 95% CI 1.19-1.42) as compared to those 67-<77 (**Table 3A and 3B and Figure 2**).

Proportional Hazards Assumption

The proportional hazards assumption was violated when comparing AVF placement (p=0.014 and p<.0001 for time and age interactions in cause-specific and subdistribution models, respectively) and maturation (p<.0001 for both models) by age. Hazards appeared proportional when comparing AVF primary patency loss (p=0.252 and p=0.904) and abandonment (p=0.954 and p=0.400).

DISCUSSION

To our knowledge, this study is the first national study in the older hemodialysis patients examining the association of age with AVF placement, maturation, and patency loss accounting

for the competing events of death, kidney transplant, and peritoneal dialysis transfer. Among the U.S. older adults who initiated dialysis with a CVC, patients ≥ 77 years old had significantly lower probability of getting an AVF placed in 3 years after dialysis initiation and matured in 2 years after placement compared to those aged 67-<77. However, in the subcohort of patients with a matured AVF, AVF primary and secondary functional patency was not statistically different by age group (67-<77 vs. ≥ 77) in 2 years after maturation.

These results are consistent with two national studies of effect of age on AVF placement and maturation among older adults initiating dialysis. [18,19] Lily et al. showed among the U.S. patients who initiated hemodialysis between 2005 and 2009, those aged 85 years and older had a lower odds of AVF maturation as compared to patients aged 65-<85 at their first dialysis session.[18] Similarly, Harford et al. reported the odds of AVF maturation was significantly lower in ≥80 group compared to those aged 67-<80 at dialysis initiation between 2005 and 2010. [19] The effect of age on AVF maturation persisted in these two studies after adjusting for patient's demographics, comorbid conditions, insurance status, prior nephrologist care patterns, BMI or functional status. However, these two studies estimated rate of AVF maturation in a cross-sectional design without considering whether these patients had an AVF placed. Our study, instead, implemented a retrospective design and considered change in the risk set due to competing events so that we obtained a better estimation of impact of age on AVF placement and maturation. Furthermore, studies by Lily and Harford examined AVF maturation at dialysis initiation so AVFs included in their studies were placed prior to dialysis. Our study extended their analyses by assessing AVF placement and maturation among older adults who initiated dialysis without a permanent vascular access. Compared to those dialyzed with an AVF or AVG, these patients are more susceptible to the greatly increased risk of infection-related

hospitalizations and all-cause mortality due to CVC use. [20] Our findings of differentiate rates in AVF placement and maturation by age provided valuable information for future vascular access planning and policy making in this particular group.

Our findings concur with the conclusions drawn from three retrospective single-center studies that older age did not increase the risk of AVF patency loss.[21, 22, 23] In a single-center study of 335 patients, Swindlehurst et al. reported the 25-month AVF primary and secondary patency rates were not significantly different between adult patients ≥65 years old and those <65.[21] Another study by Weale et al. also indicated age group (<65, 65 to 79, ≥80) was not associated with the 1- and 2-year primary and secondary patency among 658 adult patients.[22] Similar to our study, these two studies included both radiocephalic (wrist or forearm) and brachiocephalic (upper arm) AVFs. Nonetheless, patients in these two studies were enrolled after ultrasound vessel screening so they were more likely to have homogeneous vein parameters regardless of age. In the third study of 444 incident AVF patients by Lok et al., preoperative vein mapping was not necessarily performed. Their study also proved the 1- and 5- year AVF secondary patency was not significantly different between patients ≥65 and <65.[23] Our study added to the evidence by extending the findings from these single-center studies to a national cohort of patients from dialysis facilities with distinct practice patterns at various geographic locations.

Our study revealed that patients aged 77 and older had lower probability of AVF placement and maturation as compared to those aged 67-<77 after controlling for patient's demographic, comorbid conditions, functional status, and facility practice patterns. Notably, even though a greater number of patients in the age ≥77 group were removed from the risk set due to the competing events, the resulting cumulative incidence of AVF placement and

maturation were still lower than that in the 67-<77 group. This indicated the unwillingness of dialysis facilities to refer patients in this age group to AVF placement and the lower likelihood of AVF maturation even though patients in the ≥ 77 group have comparable comorbid profile and functional status as their younger counterparts. Our study showed these patients are more likely to experience a competing event than have an AVF placed or matured. Our study also demonstrated, once matured, AVFs placed in those aged ≥77 attained similar primary and secondary patency as compared to those in aged 67-<77. This suggested AVF maturation is the greatest barrier between the initial step of AVF placement and achieving the goal of patency attainment. In other words, the decision of "Fistula First" in older dialysis patients should be made based on the estimated likelihood of AVF maturation.

Nationally, the average life expectancy for patients on dialysis aged 80 to 84, and 85 years and older were 2.7 and 2.2 years, respectively.[1] Even matured, AVF use in patients ≥ 77 years old for a short period of time may not worth the risk of dialyzing with a CVC while waiting for AVF to mature. For dialysis patients approaching eighty year old, AVG may be a better alternative since it takes much less time to reach successful use (~ 2 to 4 weeks) and the associated all-cause mortality were not significantly different from that of AVF placement.[24] On the other hand, our study supports placing AVF as the initial vascular access in patients 67 to 76 years old. Hemodialysis patients aged 70 to 74 and 75-79 are expected to live up to 3.8 and 3.3 years on average.[1] If life expectancy estimated based on an individual's frailty, clinical situation, and comorbid condition is more than 2 years, AVF placement might bring overall benefits.

Our study has several strengths. Competing risk is a crucial consideration in studies of older adults undergoing dialysis because of high mortality and frequent switch in therapy. Methods which fail to account for the presence of these competing risks like standard survival

analysis can overestimate the probability of AVF outcomes.[25] In this study, we used the cumulative incidence competing risk estimate and competing risk regressions to determine the association of age and AVF outcomes. Compared to the method using traditional survival analysis, our study provided precise estimations of effects of age on AVF outcomes and printed a full picture to better describe data and interpret results. Moreover, the cutoff values of age were often arbitrarily selected in previous studies so that the effect of age on AVF outcomes was forced to be homogenous within each category. Our study, instead, chose the cutoff point of 77 to categorize age based on the change in the slope of the log hazard ratio function.

However, several limitations should be noted. First, we relied on AVF modifier codes or types of access used on the reported dialysis session to ascertain AVF maturation and patency. These codes were submitted by dialysis facilities for billing purpose and thus likely to be subjected to misclassification and selection bias. Secondly, although we adjusted for all available patient characteristics measured in claims data, it is possible that poorer vascular access outcomes among patients who initially received an AVF is the result of other factors (e.g. AVF location[28] and vein diameter[26,27]) instead of patient demographics and comorbid conditions. Unmeasured confounding likely exist since USRDS does not collect all known risk factors which are associated with choice of vascular access and AVF outcomes.

In conclusion, our retrospective analysis of a nation cohort encompassing older adults who initiated dialysis with a CVC shows increased age is associated with reduced probabilities of AVF placement and maturation but not AVF primary and secondary patency loss. In clinical practice, the likelihood of AVF maturation should be the most important consideration for vascular access planning in older hemodialysis recipients. For older patients approaching or over eighty years old, AVG could be an alternative primary vascular access. Future studies are needed

to better predict AVF maturation in this population and to improve shared decision-making process for access planning aimed at improving patient outcomes.

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Table 1. Patient demographics, comorbid conditions, functional status, lab values, and care patterns by age groups in old patients initiating dialysis with a catheter.

	Age at dialysis initiation	
	67-<77	**≥77**
Total		
Demographics		
Gender		
Male	11,526(53.1)	11,464(51.8)
Female	10,196(46.9)	10,665(48.2)
Race		
White	15,660(72.1)	17,407(78.7)
Black	5,042(23.2)	3,705(16.7)
Other/unknown	1,020(4.7)	1,017(4.6)
Region		
Northeast	3,425(15.8)	4,356(19.7)
Midwest	5,344(24.7)	5,673(25.6)
South	8,864(40.8)	7,936(35.9)
West	3,938(18.1)	4,041(18.3)
Comorbid conditions		
Comorbid score	8.8±4.6	9.5±4.5
Primary cause of renal failure		
Hypertension/Large vessel disease	6,191(28.5)	9,263(41.9)
Diabetes	9,917(45.7)	7,107(32.1)
Glomerulonephritis	656(3)	695(3.1)
Other	4,958(22.8)	5,064(22.9)
Diabetes	15,452(71.1)	13,194(59.6)
Hypertension	15,824(72.9)	16,740(75.7)
Coronary artery disease	13,259(61)	14,580(65.9)
Myocardial infarction	5,531(25.5)	5,816(26.3)
Atherosclerosis	12,731(58.6)	14,019(63.4)
Coronary revascularization	1,386(6.4)	1,190(5.4)
Congestive heart failure	14,476(66.6)	16,143(73)
Peripheral vascular disease	11,023(50.8)	12,029(54.4)
Cerebrovascular disease	6,544(30.1)	7,050(31.9)
Stroke	2,880(13.3)	2,985(13.5)
Chronic obstructive pulmonary disease	8,257(38.1)	8,565(38.7)
Cancer	4,165(19.2)	4,786(21.6)
Depression	3,984(18.3)	3,649(16.5)
Dementia	1,230(5.7)	2,397(10.8)
Functional status		
Amputation	448(2.1)	225(1)
Inability to ambulate	2,515(11.6)	3,063(13.8)
Inability to transfer	1,488(6.9)	1,854(8.4)
Needs assistance with daily activities	4,122(19)	5,447(24.6)
Institutionalized	3,191(14.7)	4,612(20.8)
Lab values		
Body mass index (kg/m^2)(mean±SD)	29.4±7.8	27±6.6

Hemoglobin (g/dl, mean ± SD)	10.1±16	10±11.2
Serum albumin (g/dl, mean ± SD)	3.1±4.3	3.1±3.1
eGFR (ml/min/1.73 m^2, mean ± SD)*	13.2±5.8	13.9±5.7
Care patterns		
Nephrology care		
No or less than 6 months	14,463(66.6)	14,661(66.3)
6-12 months	3,204(14.8)	3,151(14.3)
12 months	4,055(18.7)	4,317(19.5)
Facility type		
Hospital-based	1,956(9)	2,089(9.5)
Freestanding	19,716(91)	19,985(90.5)
Profit status		
For-profit	18,143(83.7)	18,287(82.8)
Non-profit	3,348(15.5)	3,565(16.2)
Unknown	181(0.8)	222(1)

*eGFR: estimated glomerular filtration rate.

Table 2. Numbers and percentages of arteriovenous fistula (AVF) outcomes including AVF placement in 3 years after dialysis initiation, AVF maturation in 2 years after placement, and AVF primary patency loss and abandonment in 2 years after maturation by age group in hemodialysis patients aged 67 and older.

	AVF placement	Died/TX/PD before AVF placement	No event
Total	17,271(39.4)	17,897(40.8)	8,683(19.8)
67-<77	9,074(41.8)	7,852(36.2)	4,796(22.1)
≥77	8,197(37)	10,045(45.4)	3,887(17.6)
	AVF maturation	**Died/TX/PD before AVF maturation**	**No event**
	10,260(68.9)	3,029(20.3)	1,603(10.8)
67-<77	5,527(71.5)	1,369(17.7)	834(10.8)
≥77	4,733(66.1)	1,660(23.2)	769(10.7)
	AVF primary patency loss	**Died/TX/PD before AVF primary patency loss**	**No event**
	5,664(75.2)	1,045(13.9)	819(10.9)
67-<77	2,957(74.6)	530(13.4)	475(12)
≥77	2,707 (75.9)	515(14.4)	344(9.7)
	AVF abandonment	**Died/TX/PD before AVF abandonment**	**No event**
	1,899(25.2)	2,137(28.4)	3,492(46.4)
67-<77	984(24.8)	961(24.3)	2,017(50.9)
≥77	915(25.7)	1,176(33)	1,475(41.4)

TX: Kidney transplantation; PD: Peritoneal dialysis.

Table 3A. Cause-specific hazard ratios (cHRs) and their associated 95% confidence intervals (CIs) of arteriovenous fistula (AVF) outcomes and competing events by age group in hemodialysis patients aged 67 and older.

	AVF Outcomes		Competing Events[5]	
	Unadjusted cHR (95% CI)	**Adjusted cHR (95% CI)**	**Unadjusted cHR (95% CI)**	**Adjusted cHR (95% CI)**
AVF placement[1]				
67-<77	1	1	1	1
≥77	0.93(0.90,0.96)	0.96(0.92,0.99)	1.36(1.32,1.40)	1.19(1.15,1.24)
AVF maturation[2]				
67-<77	1	1	1	1
≥77	0.95(0.91,0.99)	0.95(0.91,0.99)	1.33(1.24,1.43)	1.17(1.08,1.26)
AVF primary patency loss[3]				
67-<77	1	1	1	1
≥77	1.05(1.00,1.11)	1.05(1.00,1.11)	1.44(1.25,1.65)	1.12(0.99,1.27)
AVF abandonment[4]				
67-<77	1	1	1	1
≥77	1.07(0.98,1.17)	1.05(0.95,1.15)	1.48(1.35,1.61)	1.33(1.22,1.46)

Note: 1. Adjusted by gender, race, diabetes, hypertension, stroke, myocardial infarction, coronary revascularization, congestive heart failure, cardiovascular disease, cancer, comorbid score, body mass index (BMI), albumin, estimated glomerular filtration rate (eGFR), functional status, nephrology care, and region.

2. Adjusted by gender, race, diabetes, myocardial infarction, stroke, cardiovascular disease, functional status, facility type, comorbid score, BMI, eGFR, time of central venous catheter (CVC) dependency, and primary or secondary AVF.

3. Adjusted by gender, race, chronic obstructive pulmonary disease (COPD), depression, region, facility type, facility profit status, comorbid score, and eGFR.

4. Adjusted by gender, race, hypertension, angina and atherosclerosis, congestive heart failure, peripheral vascular disease (PVD), stroke, COPD, cancer, depression, functional status, facility type, comorbid score, BMI, eGFR, and time of CVC dependency.

5. Competing events included death, kidney transplantation, and peritoneal dialysis transfer.

Table 3B. Subdistribution hazard ratios (cHRs) and their associated 95% confidence intervals (CIs) of arteriovenous fistula (AVF) outcomes and competing events by age group in hemodialysis patients aged 67 and older.

	AVF Outcomes		Competing Events[5]	
	Unadjusted sHR (95% CI)	Adjusted sHR (95% CI)	Unadjusted sHR (95% CI)	Adjusted sHR (95% CI)
AVF placement[1]				
67-<77	1	1	1	1
≥77	0.86(0.84,0.89)	0.92(0.89,0.95)	1.36(1.32,1.40)	1.20(1.16,1.25)
AVF maturation[2]				
67-<77	1	1	1	1
≥77	0.91(0.87,0.94)	0.93(0.90,0.97)	1.35(1.25,1.45)	1.19(1.10,1.28)
AVF primary patency loss[3]				
67-<77	1	1	1	1
≥77	1.03(0.98,1.08)	1.04(0.99,1.09)	1.09(0.97,1.23)	1.04(0.92,1.18)
AVF abandonment[4]				
67-<77	1	1	1	1
≥77	1.04(0.95,1.14)	1.03(0.94,1.13)	1.43(1.31,1.56)	1.30(1.19,1.42)

Note: 1. Adjusted by gender, race, diabetes, hypertension, stroke, myocardial infarction, coronary revascularization, congestive heart failure, cardiovascular disease, cancer, comorbid score, body mass index (BMI), albumin, estimated glomerular filtration rate (eGFR), functional status, nephrology care, and region.

2. Adjusted by gender, race, diabetes, myocardial infarction, stroke, cardiovascular disease, functional status, facility type, comorbid score, BMI, eGFR, time of central venous catheter (CVC) dependency, and primary or secondary AVF.

3. Adjusted by gender, race, chronic obstructive pulmonary disease (COPD), depression, region, facility type, facility profit status, comorbid score, and eGFR.

4. Adjusted by gender, race, hypertension, angina and atherosclerosis, congestive heart failure, peripheral vascular disease (PVD), stroke, COPD, cancer, depression, functional status, facility type, comorbid score, BMI, eGFR, and time of CVC dependency.

5. Competing events included death, kidney transplantation, and peritoneal dialysis transfer.

Figure 1. Development of three study cohorts.

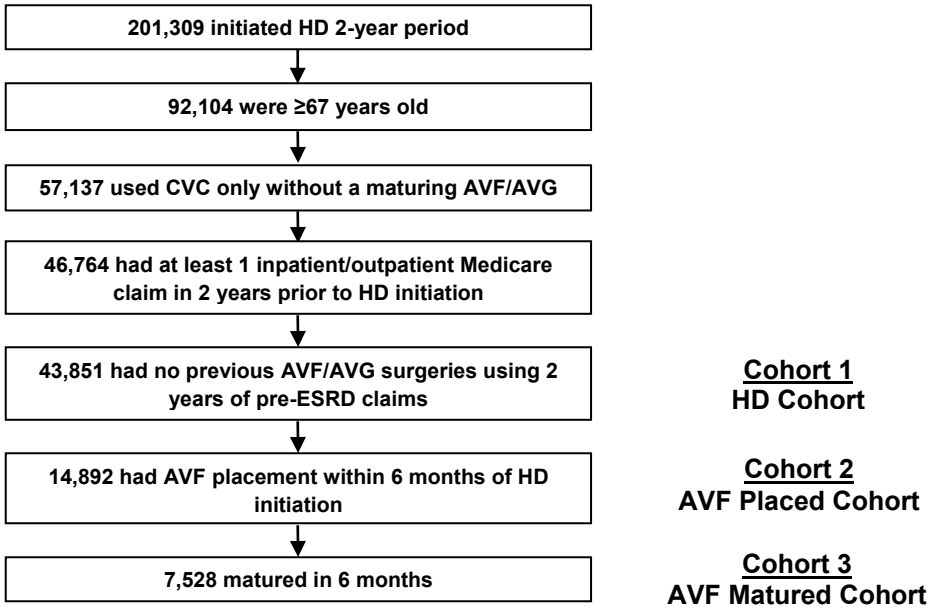
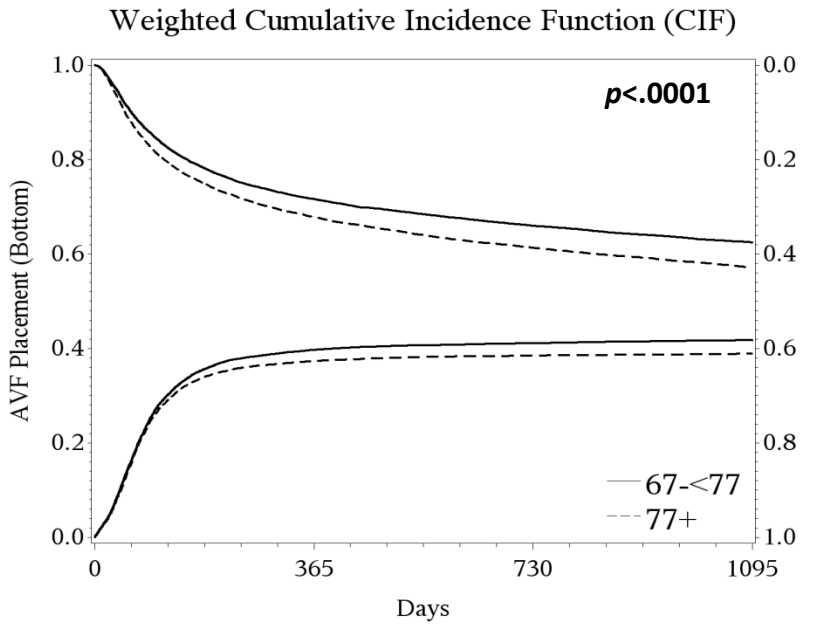
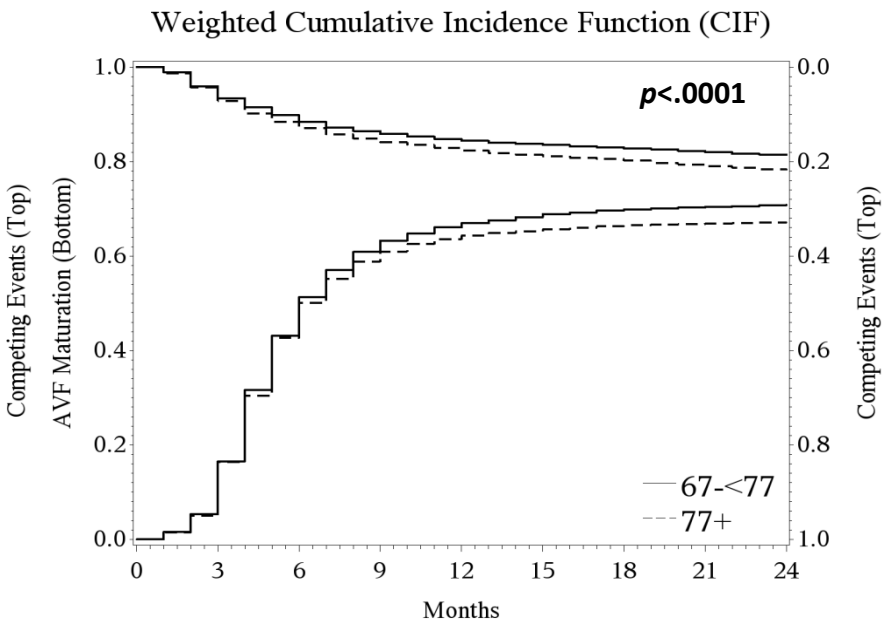
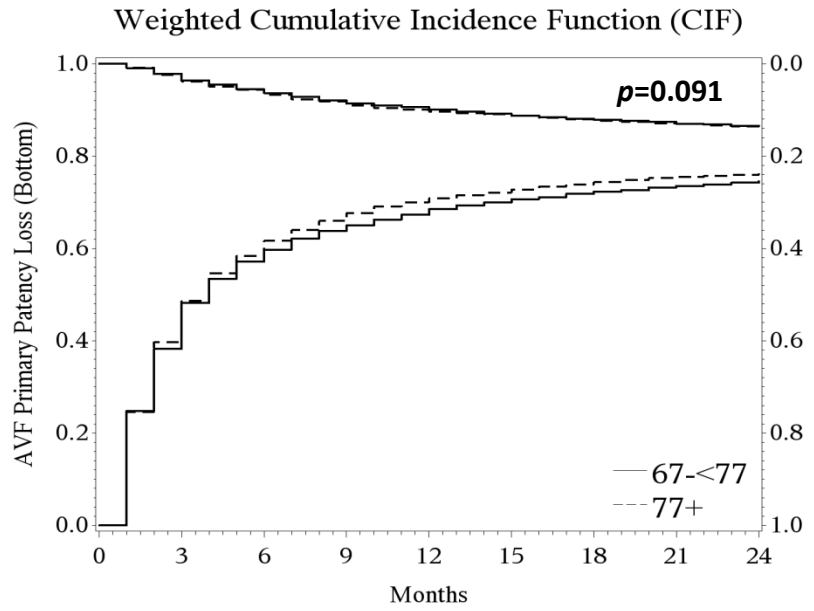

201,309 initiated HD 2-year period
92,104 were ≥67 years old
57,137 used CVC only without a maturing AVF/AVG
46,764 had at least 1 inpatient/outpatient Medicare claim in 2 years prior to HD initiation
43,851 had no previous AVF/AVG surgeries using 2 years of pre-ESRD claims
Cohort 1
HD Cohort
14,892 had AVF placement within 6 months of HD initiation
Cohort 2
AVF Placed Cohort
7,528 matured in 6 months
Cohort 3
AVF Matured Cohort

Figure 2. Weighted cumulative incidence functions (CIF) of arteriovenous fistula (AVF) outcomes and competing events by age group in hemodialysis patients aged 67 and older. *P* values were obtained from Gray's test for equality of weighted CIF. Bottoms lines: AVF outcomes including AVF placement in 3 years after dialysis initiation, AVF maturation in 2 years after placement, AVF primary patency loss in 2 years after maturation, and AVF abandonment in 2 years after maturation; top lines: competing events including death, kidney transplant, and transfer to peritoneal dialysis.


Weighted Cumulative Incidence Function (CIF)
p<.0001
AVF Placement (Bottom)
Competing Events (Top)
67-<77
77+
Days
0
365
730
1095


Weighted Cumulative Incidence Function (CIF)
p<.0001
AVF Maturation (Bottom)
Competing Events (Top)
67-<77
77+
Months


Weighted Cumulative Incidence Function (CIF)
p=0.091
AVF Primary Patency Loss (Bottom)
Competing Events (Top)
67-<77
77+
Months

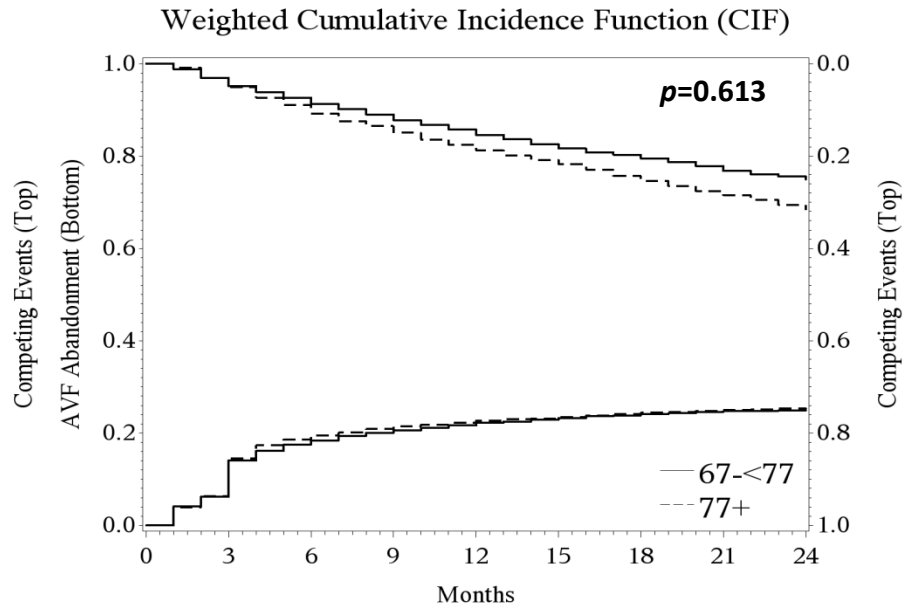
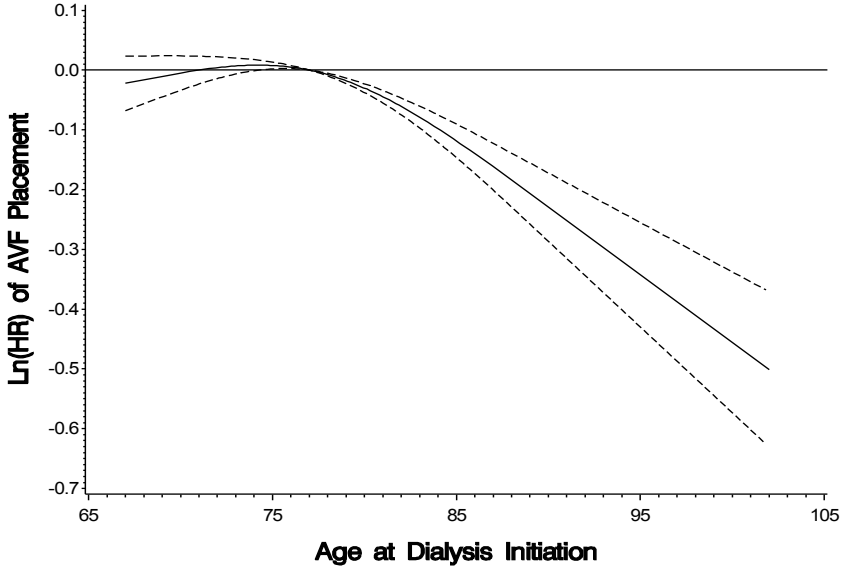
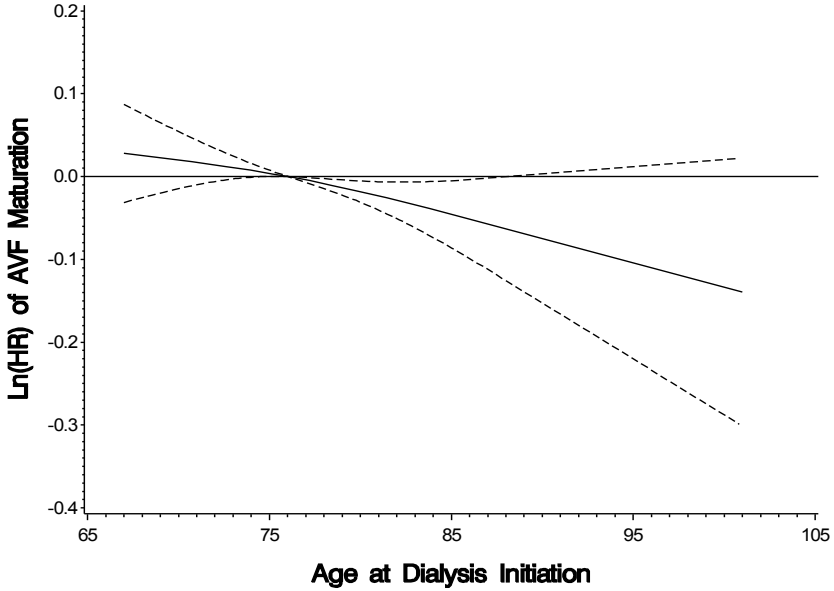

Weighted Cumulative Incidence Function (CIF)
p=0.613
AVF Abandonment (Bottom)
Competing Events (Top)
67-<77
77+
Months

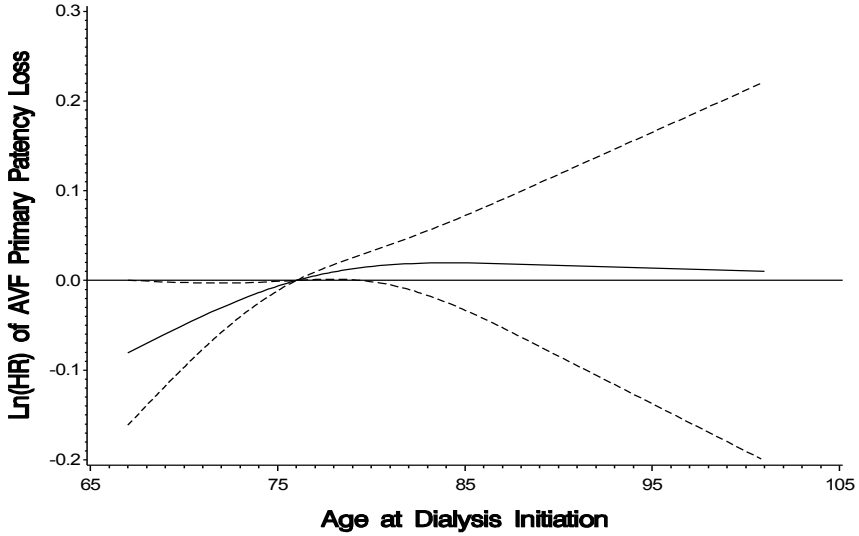
Table S1. Codes of surgical and endovascular procedures associated with hemodialysis arteriovenous fistula (AVF) management.

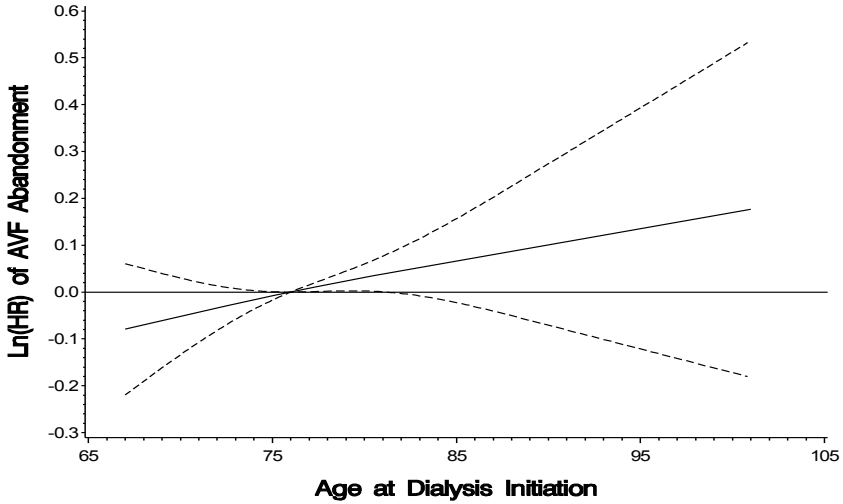
Type of intervention	Codes
Open surgical procedures	**CPT-4 Codes**
Revision, open, arteriovenous fistula; with thrombectomy, autogenous or nonautogenous dialysis graft	36833
Revision of fistula or graft	36832
Fistula elevation or superficialization	36832
Ligation of accessory veins	36832
Open surgical procedures for treatment of steal syndrome	36832
Open repair of pseudoaneurysm	36832
Banding fistula or graft	36832
Open thrombectomy, arteriovenous fistula without revision, autogenous or nonautogenous dialysis graft	36831
Endovascular interventions	**CPT-4 Codes**
Angiogram with venous angioplasty	36147, 35476, 75978
Angiogram with arterial angioplasty	36147, 35475, 75962
Angiogram with venous angioplasty and stent	36147, 37205, 37206 (rarely +37239)
Angiography, arteriovenous shunt (e.g., dialysis patient fistula / graft)	75791 (must be present with other interventions)
Percutaneous thrombectomy	36870 (also 36147, 36148)
Percutaneous thrombectomy with venous angioplasty	36870, 36147, 36148, 35476, 75978
Percutaneous thrombectomy with arterial angioplasty	36870, 36147, 36148, 35475, 75962
Percutaneous thrombectomy with venous angioplasty and stent	36870, 36147, 36148, 37205, 37206 (rarely +37239)
Inpatient procedures	**ICD-9 Codes**
Compression of vein	459.2
Mechanical complications of vascular device, implant and graft	996.1
Other complication of vascular device, implant and graft	996.7

F**igure S1.** Restricted cubic spline plots of log hazard ratio of arteriovenous fistula (AVF) outcomes versus age with 3 knots at 10th, 50th, and 90th percentile. A restricted cubic spline is a cubic spline in which the splines are constrained to be linear in the two tails. Break points in the linearity are changes in slope for the log hazard ratio function. The dotted curves represent the 95% confidence intervals. (A) AVF placement in 3 years after dialysis initiation; (B) AVF maturation in 2 years after placement; (C) AVF primary patency loss in 2 years after maturation; (D) AVF abandonment in 2 years after maturation.


Ln(HR) of AVF Placement
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
65
75
85
95
105
Age at Dialysis Initiation


Ln(HR) of AVF Maturation
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
65
75
85
95
105
Age at Dialysis Initiation


Ln(HR) of AVF Primary Patency Loss
0.3
0.2
0.1
0.0
-0.1
-0.2
65
75
85
95
105
Age at Dialysis Initiation


Ln(HR) of AVF Abandonment
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
65
75
85
95
105
Age at Dialysis Initiation

CHAPTER FOUR

VALIDATION OF A RISK EQUATION PREDICTING HEMODIALYSIS ARTERIOVENOUS FISTULA PRIMARY FAILURE IN ELDERLY

ABSTRACT

Background: Choice of vascular access for older hemodialysis patients presents a special challenge since the rate of arteriovenous fistula (AVF) primary failure is high. Although the Lok's risk equation for AVF primary failure has achieved good prediction accuracy and holds great potential for clinical use, it has not been validated in the U.S. older hemodialysis patients. ***Methods:*** We assembled a validation data set of 14,892 patients aged 67 years and older who initiated hemodialysis with a central venous catheter between 7/1/2010 and 6/30/2012 and had a subsequent, incident AVF placement from the United States Renal Data System. We examined the external validity of Lok's model by applying it to the validation data set. The discriminatory accuracy and calibration were evaluated by the concordance index (C-statistics) and calibration plot, respectively. ***Results:*** The observed frequency of AVF primary failure varied from 0.45 to 0.53 in hemodialysis patients in the validation data set. The predicted probabilities of AVF primary failure calculated by using the Lok's risk equation ranges from 0.08 to 0.61 and 77.8%, 40.5%, and 51.7% of patients were categorized as having high, intermediate, and low risk of AVF primary failure, respectively. C-statistics of the Lok's risk equation in the validation data set was 0.53 (95% CI: 0.52 - 0.54). The predicted probabilities of AVF primary failure corresponded poorly with the observed proportions In the calibration plot. ***Conclusions:*** When externally applied to a cohort of the U.S. older hemodialysis patients, the Lok's risk equation exhibited poor discrimination and calibration accuracy. It is invalid to use it to predict AVF primary failure. A more complex model with strong predictors is expected to better serve clinical determination for AVF placement in this population.

INTRODUCTION

Annually over 50,000 patients who are 65 years and older start hemodialysis in the United States. Choosing the primary vascular access for older dialysis patients is challenging. Although current clinical guidelines and the "Fistula First" campaign recommend arteriovenous fistula (AVF) as the optimal type of vascular access,[1,2] older age is associated with higher probability of AVF primary failure.[3] A failed AVF requires one or more salvage procedures to promote maturation which leads to prolonged dialysis dependence on central venous catheter (CVC). CVC is known as the most inferior vascular access type and associated with substantially elevated rates of infection[4,5,6] and all-cause mortality.[7] For older patients at great risk of AVF failure, an arteriovenous graft (AVG) might be an alternative vascular access choice for dialysis. A model which accurately predicts AVF primary failure in older dialysis patients based upon patient characteristics can assist better clinical decision-making for AVF placement.

To date, few studies have especially developed models to predict AVF primary failure for older dialysis patients. The Lok's risk equation for AVF primary failure was derived from a retrospective cohort of 422 Canadian hemodialysis adults with a first-time AVF placement.[8] Compared with other available prediction models, the Lok's risk equation holds great potential for clinical use. The equation incorporates 4 binary predictors (patient age $\geq$ 65, white race, and history of peripheral vascular disease (PVD) and coronary artery disease (CAD)) which can be easily collected in clinical setting. A simple version of this equation has a clinical-friendly algorithm produces a score ranging from 0 to 10.5. A score < 2.0 is deemed as having low risk of AVF primary failure, 2 - 3, moderate risk, 3.1- 7.9, high risk, and > 8, very high risk. However, this equation was not especially developed from or for older patients. Applying it to the U.S. older dialysis patients provides valuable information. The objective of this study is to validate the Lok's risk equation for AVF primary failure in the U.S. older hemodialysis patients.

METHODS

Validation Data Set

Our primary data source was derived from the 2010-2013 United States Renal Data System (USRDS) standard analytic files (SAFs). We assembled our validation data set by extracting end stage renal disease (ESRD) patients aged 67 years and older who initiated hemodialysis with a CVC without a maturing AVF or AVG present between 7/1/2010 and 6/30/2012 from Medical Evidence Form (**Figure 1**). Patients who did not have any Medicare inpatient or outpatient claim and those who had one or more vascular access placements (either AVF or AVG) in the two-year period prior to dialysis initiation were excluded. We further identified patients who had an AVF placement within 6 months of dialysis initiation by using CPT-4 codes of 36818, 36819, 36820, 36821, and 36825 from physician/supplier claims file. The final validation data set included 14,892 patients.

Study Outcome

The primary outcome of this study was AVF primary failure. We used the same definition of primary failure from Lok et al. - an AVF that was unable to be used for dialysis for a month within 6 months of its placement, despite interventions to facilitate its use – to define this outcome. It was ascertained as absence of vascular access modifier code 'V7' (AVF) from the institutional details claims file or absence of AVF with two needles reported from the Crownweb clinical file. Patients were followed for six months from the date of AVF placement.

Study Predictors

AVF primary failure was expressed as a function of four binary variables in the Lok's risk equation as: Logit (primary failure) = -2.0809 + 0.6907 x (age ≥ 65) + 0.9821 x (PVD) + 0.8576 x (CAD) -1.0496 x (white).[9] Lok et al. defined CAD as "coronary stenosis by angiography or history of myocardial infarction or previous coronary revascularization by angioplasty, stenting, or bypass surgery". According to this definition, we determined a diagnosis of CAD by (1) myocardial infarction; (2) other forms of chronic ischemic heart disease including angina, coronary atherosclerosis and stenosis; and (3) coronary revascularization. To maximally capture patient's existing diseases, we used one inpatient or outpatient diagnosis code (either primary or secondary) in the pre-ESRD institutional claims and physician/supplier claims 2 years prior to dialysis to ascertain PVD, CAD, and other comorbidities. **Table S1** lists all diagnosis codes we used. We obtained patient's age at dialysis initiation and race, primary cause of renal failure, pre-dialysis nephrology care patterns from Medical Evidence Form. Duration of CVC dependency was calculated as time from dialysis initiation to AVF placement.

Statistical Analysis

Patient characteristics and practice patterns were summarized in total. We calculated the predicted probabilities of AVF primary failure for each patient based on the Lok's risk equation and assigned each patient into a risk category accordingly: high risk if the predicted value is ≥ 40%; intermediate if 20 - 40%; and low if < 20%. We assessed the external validity of the Lok's model in older patients by applying it in the validation data set with the original regression coefficients. The discriminatory accuracy of the Lok's model was evaluated by C-statistics, also known as the area under the receiver-operating characteristic curve (AUC). The value of C-statistics corresponds to the probability that a randomly selected patient with the risk factors has

a higher predicted risk of AVF primary failure than a randomly selected patient without the risk factors.[10,11] A value of 1.0 indicates that the score assigned by the model perfectly discriminates patients with different outcomes, while a value of 0.5 indicates that the scoring model contains no predictive information. Generally, models with a C-statistic greater than 0.70 are considered to have good discriminative ability and those greater than 0.80 are excellent. We used patient's age at dialysis initiation, race, and the diagnosis of PVD and CAD within two years prior to dialysis to calculate the expected probability of AVF primary failure for each patient. Calibration of the model was examined by comparing the agreement between the predicted probabilities and the observed proportions of AVF primary failure in a calibration plot.[12]

RESULTS

Baseline Characteristics

The validation data set was comprised of 14,892 U.S. patients aged 67 years or older who initiated hemodialysis with a CVC and had a subsequent AVF placement. **Table 1** presented patient demographics, comorbid conditions, and quality of care in the study cohort. The mean age of the patient population was 76.7 years old with 54.5 % of male and 76.0 % of White. The population carried heavy disease burdens: 68.7% of them had diabetes, 86.2% had hypertension, 64.0% had CAD, and 52.7% had PVD. The mean time from dialysis initiation to AVF placement was 70.8 days and 45.7% of patients started hemodialysis without any pre-dialysis nephrology care.

Observed and Predicted Probability of AVF Primary Failure

Among 14,892 patients, 7,374 (49.5%) had AVF primary failure within 6 months of AVF placement (**Table 1**). Patients who experienced AVF primary failure were more likely to be female and black race. Compared with those with matured AVFs, they carried more comorbid burdens (diabetes 42.7% vs. 41.1%; myocardial infarction 26.4% vs. 22.9%; history of stroke 13.0% vs. 11.0%) and had less pre-dialysis nephrology care (no nephrology care 46.3% vs. 45.0%). The number and percentage of patients in each risk category of predicted probabilities of AVF primary failure were listed in **Table 2**. A total of 7.7% patients were considered as having high risk of primary failure. Their predicted probability and observed frequency of AVF primary failure was 0.61 and 0.53, respectively. A total of 40.5% of patients were in the intermediate category and 51.7% were in the low risk category. The predicted risk of AVF primary failure among patients in the intermediate category ranged from 0.35 to 0.40 and their observed proportion of primary failure was from 0.51 to 0.57. Approximately 45-48% of patients who were assigned to the low risk group experienced an AVF primary failure. Their predicted probability ranged from 0.08 to 0.20.

Model Discrimination and Calibration

When the Lok's risk equation was applied to the validation data set, the C-statistics of the Lok's risk equation was 0.53 (95% CI: 0.52-0.54) (**Figure 2)**. **Figure 3** revealed the predicted probabilities of AVF primary failure corresponded poorly with the observed proportions in the calibration plot. Although the predicted risk of AVF primary failure differed significantly in each risk category, the observed frequencies of primary failure were similar. The observed frequency

of AVF primary failure in patients who had the highest predicted risk (0.61) was 0.53. The observed frequency of AVF primary failure in patients who had the lowest predicted risk (0.08) was 0.45.

DISCUSSION

Our validation study shows the Lok's risk equation for AVF primary failure performs poorly when externally applied to a national cohort of incident hemodialysis patients aged 67 years or older. The model exhibits a very low discriminative ability which nearly provides no predictive information. Calibration plot demonstrates the predicted probabilities correspond poorly with the observed percentages of AVF primary failure. The decrease in predicted accuracy is of such a degree that the model appears useless for clinical decision-making of vascular access choice in older hemodialysis patients.

Our finding that the Lok's model for AVF primary failure has low predicted accuracy when externally validated in the US older hemodialysis patients is consistent with the findings from Lilly et al.[13] They used the Lok's classification system to calculate risk scores for AVF primary failure in all U.S. adult patients at their first hemodialysis session from 2005 to 2009. Although they reported predicted probability of AVF primary failure was inversely associated with percentages of AVF maturation, the effect was small. Rate of AVF maturation varied from 19.0% in patients in the "very high" predicted risk category to 25.6% in patients in the "low" risk one. The odds of AVF primary failure were lower in adult patients from the moderate-, high-, and very high-risk categories than those in low-risk categories with odds ratio of 0.90, 0.80, and 0.68, respectively.

Various aspects need to be considered to address these results. Firstly, our validation data set is considerably larger and more diverse than the cohort in Lok's study. The Lok's risk equation was developed from a prospective cohort of 422 patients from a university-based health care program in Canada. Our validation cohort was a population of 14,892 U.S. older hemodialysis patients from nationwide dialysis facilities. The Lok's cohort included more males (67.8%). It was younger (mean age of 58) and healthier (diabetic 28.4%, hypertension 76%, CAD 32.2%, and PVD 8.3%) than our cohort (diabetic 68.8%, hypertension 86.3%, CAD 64.1%, and PVD 52.8%). More importantly, practice patterns of AVF placement have been changed dramatically since the Lok's study was published. In the study by Lok et al., AVFs were created between 1995 and 2004, while AVFs were created from 2010 to 2012 in our study. In 2003, the Centers for Medicare and Medicaid Service (CMS) launched the Fistula First Breakthrough Initiative (FFBI). In collaboration with the 18 national ESRD Networks, CMS promulgated the FFBI goal of achieving functional AVF use in greater than 65% of hemodialysis patients through its Clinical Performance Measures (CPMs) and established Quality Improvement and Patient safety (QIPS) rules.[14] After "Fistula First" campaign, dialysis facilities are inclined to assign more patients to AVF creation. Patients who are the suitable candidates for AVG creation, for example, those who have inferior vasculature, were more likely to be referred to AVF placement after "Fistula First". This practice increases the likelihood of AVF primary failure. The high rate of AVF primary failure in our cohort (49.2% versus 14% and 39% in the Lok's study, respectively, in the training and validation data set) can only be explained partly by advanced age and comorbid conditions, whereas change in clinical practice pattern is the major reason.

We expect a complex prediction model which incorporates additional variables relevant to AVF maturation increases prediction ability. For example, gender was not included in the

Lok's model because it was only borderline significant in their training data and was not statistically significant in the internal cross-validation.[9] In our data set, however, gender is significantly associated with AVF primary failure, as aligned with other studies on risk factors for AVF primary failure.[15, 16, 17] In Lily's study, several factors that dropped out the Lok's model were highly significantly including diabetes, hypertension, congestive heart primary failure, other cardiac disease, cerebrovascular disease, gender, Hispanic ethnicity, BMI, prior nephrologist care, insurance, and year maintenance hemodialysis started. Adding these variables in the prediction model probably improves the predictive accuracy for AVF maturation. It is also highly possible that the poor vascular access outcome is not only the results of patient demographics, comorbid conditions, and clinical care patterns, but other factors (e.g. AVF location, arterial diameter,[18] and vein diameter[19]). Feldman et al developed a prediction model for AVF maturation based on a cohort of 348 adult patients from 12 hospitals in the Delaware Valley Region.[20] The C-statistics for internal validation was 0.66 for the model including patient's age, diagnosis of cardiovascular disease, previous access history, mean arterial pressure <85 mm Hg, and dialysis dependency. After adding in heparin use and upstream vein diameter, the C-statistics was improved to 0.69. Robbin et al. recently established a prediction model for AVF unassisted and overall maturation based on data from Hemodialysis Fistula Maturation (HFM) Study which is a prospective, multi-center cohort study with 602 enrolled patients.[21] Their model only included three post-operative ultrasound parameters (AVF blood flow, diameter, and depth) but it exhibited strong predict ability. The C-statistics of their model was 0.69, 0.74, and 0.79, respectively, for unassisted maturation, and 0.69, 0.71, and 0.76, respectively, for overall AVF maturation at 1 day and 2 and 6 weeks after AVF placement. However, some predictors including vein and artery parameters in last two models are not

routinely collected in the USRDS data; it is impossible to validate them in this study to derive a useful clinical decision tool for AVF placement.

Despite its clear findings and the large national population used, our study has several limitations. First, we relied on AVF modifier codes or types of access used on the reported dialysis session to ascertain AVF maturation and patency. Access type reported from the dialysis claim may not reflect the AVF most frequently used for dialysis in the month. These codes were submitted by dialysis facilities for billing purpose and thus likely to be subjected to misclassification bias. Although these codes are increasingly used in recent studies, [17,22] they [14]haven't been validated. Secondly, the diagnosis of PVD and CAD and other comorbidities were determined by ICD-9 diagnosis codes which did not show disease severity and might be underreported.

CONCLUSION

In conclusion, using a national cohort of older patients who initiated hemodialysis with a CVC and had a subsequent, incident AVF placement, we have externally validated the Lok's risk equation for AVF primary failure. We found the Lok's model had inadequate discrimination or calibration ability to predict AVF primary failure in older hemodialysis patients. A more complex model with strong predictors for AVF primary failure is expected to better serve clinical determination for AVF placement in this population.

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Table 1. Baseline characteristics of the validation data set of older patients who initiated hemodialysis with a central venous catheter and had subsequent arteriovenous fistula placement (AVF).

	Total
Total cohort	**14,892**
Demographics	
Age at dialysis initiation (yrs)(mean±SD)	76.7±6.5
67-<75	6,196(41.6)
75-<85	6,641(44.6)
≥85	2,055(13.8)
Gender	
Male	8,115(54.5)
Female	6,777(45.5)
Race	
White	11,322(76.0)
Black	2,755(18.5)
Other/unknown	815(5.5)
Comorbid conditions	
Primary cause of renal failure	
Hypertension/Large vessel disease	5,453(36.6)
Diabetes	6,236(41.9)
Glomerulonephritis	527(3.5)
Other	2,676(18.0)
Diabetes	10,235(68.7)
Hypertension	12,839(86.2)
Coronary artery disease	9,533(64.0)
Myocardial infarction	3,665(24.6)
Atherosclerosis	9,227(62.0)
Coronary revascularization	854(5.7)
Congestive heart failure	10,463(70.3)
Peripheral vascular disease	7,848(52.7)
Cerebrovascular disease	4,670(31.4)
History of stroke	1,785(12)
Chronic obstructive pulmonary disease	5,757(38.7)
Cancer	2,968(19.9)
Care patterns	
CVC dependency (days, mean ± SD)	70.8±42.5
Nephrology care	
No care	6,799(45.7)
0-6 months	2,311(15.5)
6-12 months	2,393(16.1)
12 months	3,389(22.8)

Table 2. Observed probability and risk category of arteriovenous fistula (AVF) primary failure and risk predicted by the Lok's risk equation in the U.S. older hemodialysis patients.

Risk category	N(%)		PVD	CAD	White	Predicted probability of primary failure	Observed frequency of primary failure
High (≥40%)	1,152(7.7)	1,152(7.7)	Yes	Yes	No	0.61	0.53
Intermediate (20%-<40%)	6,038(40.5)	516(3.5)	Yes	No	No	0.40	0.57
		869(5.8)	No	Yes	No	0.37	0.51
		4,653(31.2)	Yes	Yes	Yes	0.35	0.52
Low (<20%)	7,702(51.7)	1,033(6.9)	No	No	No	0.20	0.48
		1,527(10.3)	Yes	No	Yes	0.19	0.47
		2,859(19.2)	No	Yes	Yes	0.17	0.49
		2,283(15.3)	No	No	Yes	0.08	0.45

*PVD: peripheral vascular disease; CAD: coronary artery disease.

Figure 1. Development of the study validation data set.

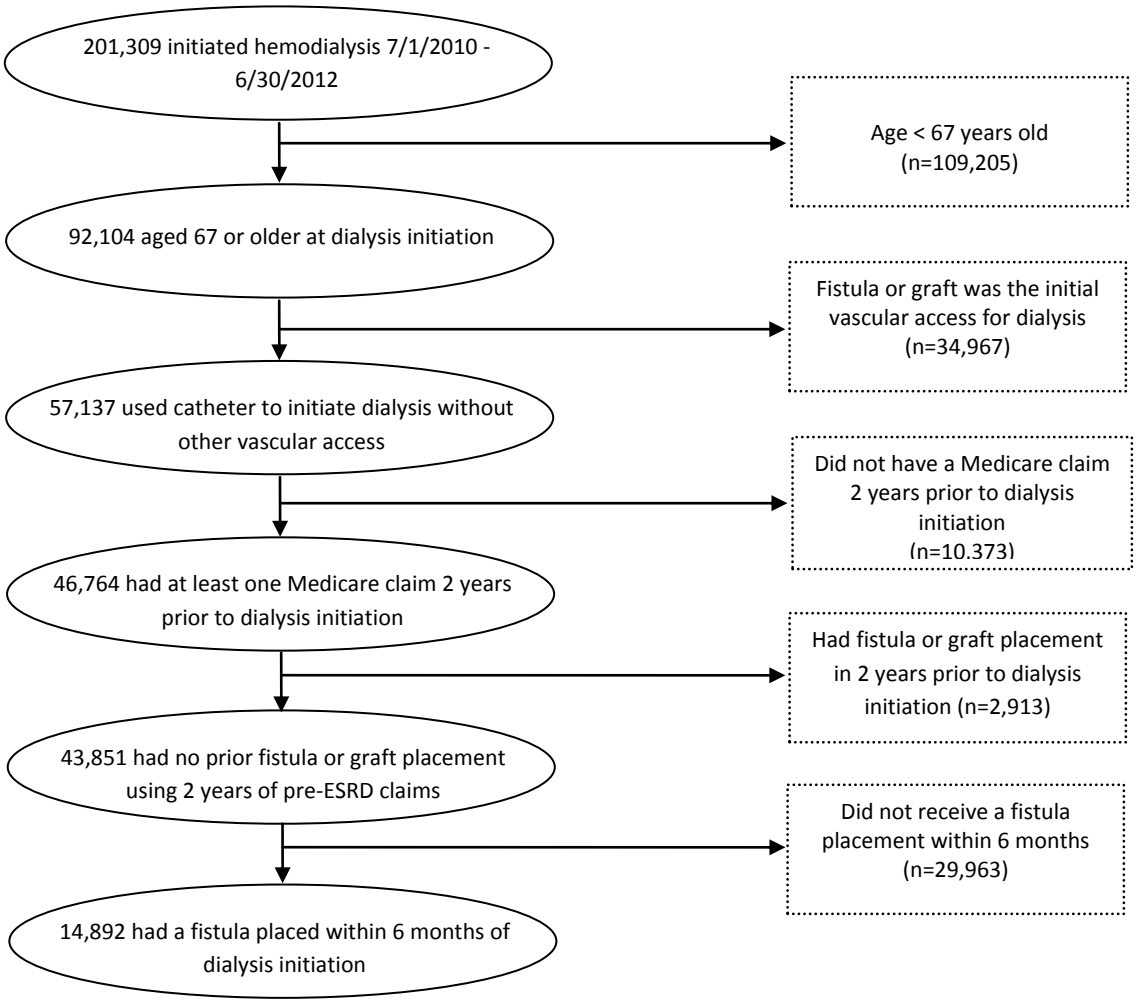
201,309 initiated hemodialysis 7/1/2010 - 6/30/2012
Age < 67 years old (n=109,205)
92,104 aged 67 or older at dialysis initiation
Fistula or graft was the initial vascular access for dialysis (n=34,967)
57,137 used catheter to initiate dialysis without other vascular access
Did not have a Medicare claim 2 years prior to dialysis initiation (n=10.373)
46,764 had at least one Medicare claim 2 years prior to dialysis initiation
Had fistula or graft placement in 2 years prior to dialysis initiation (n=2,913)
43,851 had no prior fistula or graft placement using 2 years of pre-ESRD claims
Did not receive a fistula placement within 6 months (n=29,963)
14,892 had a fistula placed within 6 months of dialysis initiation

Figure 2. Receiver operating characteristics (ROC) curves showing the discriminative accuracy of the Lok's risk equation in U.S. older patients who initiated hemodialysis with a catheter and had subsequent arteriovenous fistula (AVF) placement. The dash line: the Lok's risk equation (C-statistics 0.53; CI of 0.52-0.54). The solid diagonal line: the uninformative model.

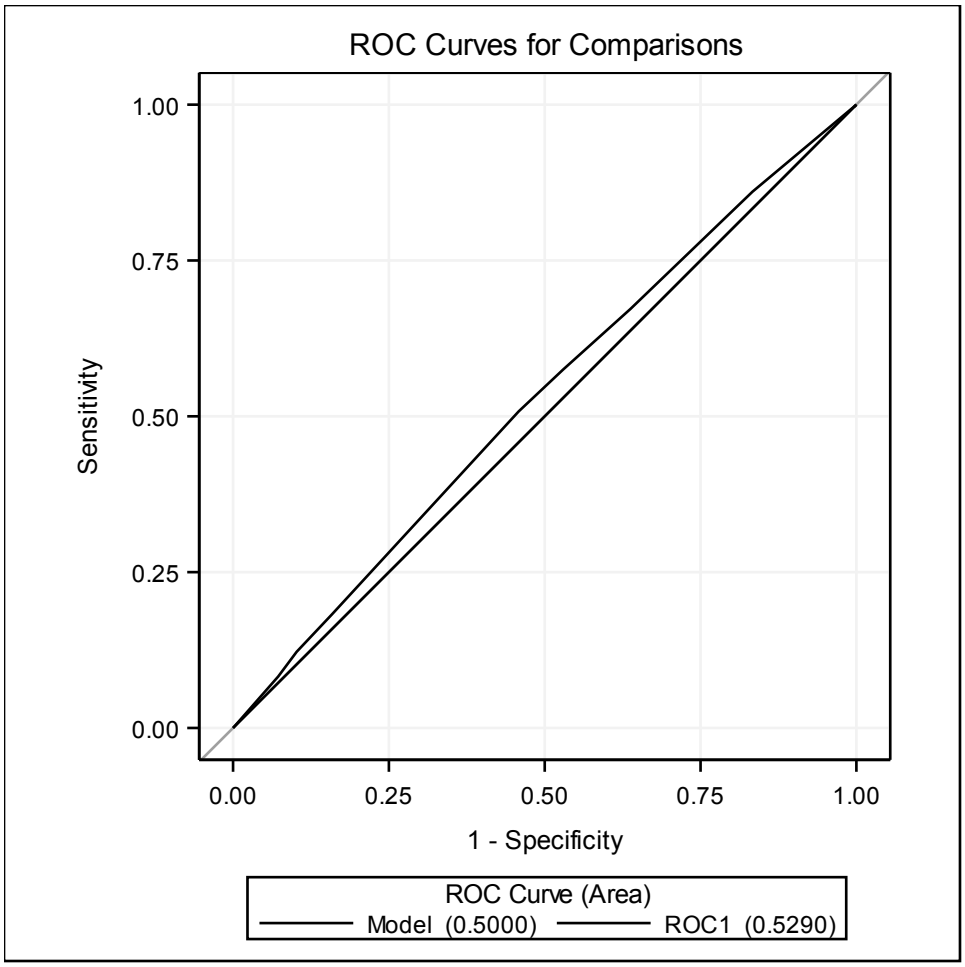
ROC Curves for Comparisons
1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
ROC Curve (Area)
Model (0.5000)
ROC1 (0.5290)

Figure 3. Calibration plot of predicted risk of arteriovenous fistula (AVF) primary failure by the Lok's risk equation. The diagonal line denotes perfect agreement between predicted risk and observed probabilities.

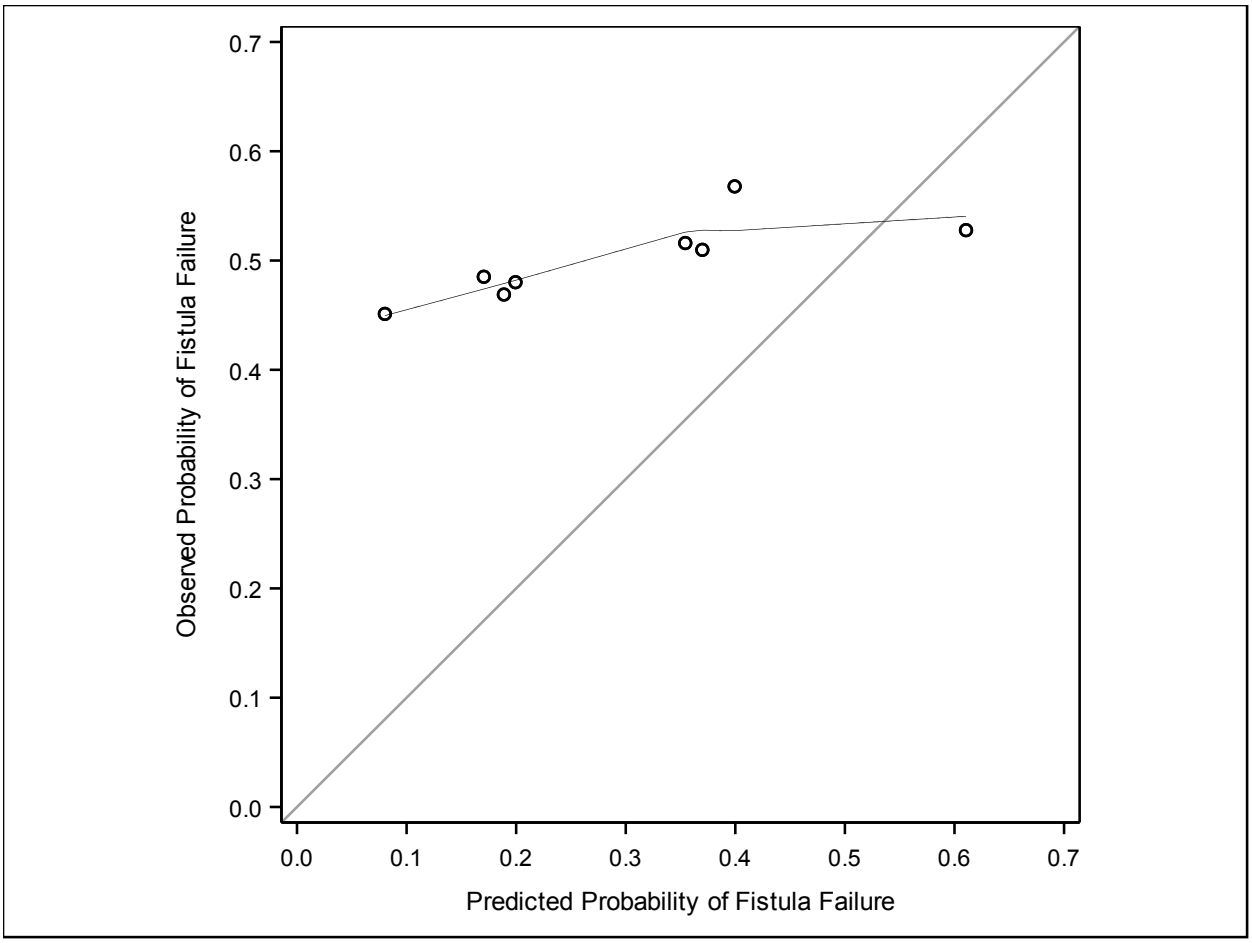
Observed Probability of Fistula Failure
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Predicted Probability of Fistula Failure
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7

Table S1. International Classification of Diseases (ICD-9) and Healthcare Common Procedure Coding System (HCPCS) codes used to identify co-morbid in the U.S. older hemodialysis patients.

Co-Morbid Events Prior to ESRD	ICD-9 Codes	HCPCS Codes
Diabetes	250,357.2,362.0,366.41	
Hypertension	401	
Coronary Artery Disease		
Myocardial Infarction	410,412	
Atherosclerosis/stenosis	413,414	
Coronary Revascularization	360,361, 00.66,v4581,v4582	9298x,3351x,3352x,92990-92996,33531-33536
Congestive Heart Failure	398.91,402.01,402.11,402.91,404.01,404.03,404.11,404.13,404.91,404.93,425.4-425.9,428	
Peripheral Vascular Disease	440-444,447,451-453,557	
Cerebrovascular Disease	362.34, 430-438	
Stroke	430,431,436,433x1,434x1	
Chronic Obstructive Pulmonary Disease	491.0,491.1,491.8,491.9,491.20,491.21,491.22,492.0,492.8,494.0,494.1,496	
Cancer	140-200	

CHAPTER FIVE

SELECTING IMPORTANT PREDICTORS FOR ARTERIOVENOUS FISTULA MATURATION IN OLDER HEMODIALYSIS PATIENTS BY USING RANDOM SURVIVAL FORESTS

ABSTRACT

Background: Placing an arteriovenous fistula (AVF) in older hemodialysis patients at great risk of AVF primary failure leads to prolonged dependency on central venous catheter (CVC) and associated inferior patient outcomes. A model which accurately predicts AVF maturation can facilitate better clinical determination for AVF placement in older hemodialysis patients. ***Methods:*** We assembled a retrospective cohort of 14,892 patients aged 67 years and older who started hemodialysis with a CVC between 7/1/2010 and 6/30/2012 and had a subsequent, incident AVF placement from the United States Renal Data System (USRDS). We randomly divided the study cohort into training (9,829, 66%) and validation data sets (5,063, 34%) and used random survival forests (RSF) with competing risks to identify important predictors for AVF maturation. ***Results:*** A total of 49.7% patients in the training data set achieved AVF maturation and 13.6% had a competing event. The median time to maturation was 4 (IQR: 3-5) months. From the RSF of 1,000 trees based on 34 variables, patient's gender had the highest variable importance (VIMP, 0.0027), followed by race, being institutionalized, days on hemodialysis without an AVF, estimated glomerular filtration rate, and body mass index with borderline importance (VIMP $\geq$ 0.0005). The out-of-bag (OOB) error rate of the RSF was 45.3% and 45.8% for AVF maturation in the training and validation data sets, respectively. ***Conclusions:*** Predictors captured in USRDS data have limited ability to predict AVF maturation. Among the available predictors, patient's gender might be considered as the most important predictor for AVF maturation.

INTRODUCTION

Clinical guidelines recommend matured arteriovenous fistula (AVF) as the optimal type of vascular access for hemodialysis patients of all ages. In older dialysis recipients, AVF, once matured, is associated with long-term benefits of greater patency and requires less interventional procedures to maintain functionality as compared to another type of permanent vascular access, arteriovenous graft (AVG).[1] Studies, however, show increased age is associated with reduced rate of AVF maturation. Nationwide, the prevalence of AVF maturation was lower in patients over 75 years (61%) as compared to those 65-74 (64%) and 45-64 (67%).[2] In the meta-analysis of AVF outcomes from 10 studies which defined elderly from >50 to >70 years old, the rate of AVF primary failure was significantly higher in elderly compared with that in nonelderly.[3] A model which accurately predicts AVF maturation in older hemodialysis patients based upon patient characteristics, comorbid conditions, and life expectancy can facilitate better clinical decision making for vascular access choice. To date, there were few existing models to predict AVF maturation especially developed for older dialysis recipients. Lok et al. established a scoring system to estimate the risk of failure of AVF maturation based on 422 Canadian adult hemodialysis patients with a first-time AVF placement.[4] This model incorporates four patient-level predictors including patient age, race, diagnosis of peripheral vascular disease and coronary artery disease and achieved a good predictive accuracy. Feldman et al. derived another model from a cohort of 348 U.S. adult hemodialysis patients from the Delaware Valley Region. In additional to patient's age and history of cardiovascular disease, their model included history of previous vascular access, mean arterial pressure, dialysis dependency, heparin use, and vein diameter to predict AVF maturation.[5] Both models, however, were developed a decade ago from regional studies for all adult patients. The aim of this study is to identify important predictors for

AVF maturation for older adults receiving hemodialysis. Developing a clinically friendly model to predict AVF maturation is critical to improve vascular access-related patient outcomes for this population.

METHODS

Study Population

Our primary data source was derived from the 2010-2013 United States Renal Data System (USRDS) standard analytic files (SAFs). We assembled our validation data set by extracting patients aged 67 years and older who initiated hemodialysis with a CVC without a maturing AVF or AVG present between 7/1/2010 and 6/30/2012 from Medical Evidence Form (**Figure 1**). Patients who did not have any Medicare inpatient or outpatient claim and those who had one or more vascular access placements (either AVF or AVG) in the two-year period prior to dialysis initiation were excluded. We further identified patients who had an AVF placement within 6 months of dialysis initiation by using CPT-4 codes of 36818, 36819, 36820, 36821, and 36825 from physician/supplier claims file. The final validation data set included 14,892 patients.

Study Outcome and Competing Events

The primary outcome of this study was AVF maturation. It was defined as an AVF can be used with two-needle cannulation for two-thirds or more of all prescribed dialysis for one month. We ascertained AVF maturation as presence of vascular access modifier code 'V7' (AVF) from the institutional details claims file or presence of AVF with two needles reported from the Crownweb clinical file. Patients who died, switched to peritoneal dialysis, or received a kidney transplant without evidence of AVF maturation were treated as experiencing competing events.

They were identified by using the death file, transplant file and dialysis institutional claims file, respectively. Patients were followed from the date of AVF placement to AVF maturation, competing events, or 6 months after AVF placement, whichever came first.

Study Predictors

We selected 34 candidate predictors based on the existing literature of AVF maturation and their availability in the USRDS data. From the Medical Evidence Form, the following potential risk factors were extracted at dialysis initiation: patient demographics (age, gender, and race), residential region (New England, Mid-Atlantic, West, Southwest, Midwest, and South), functional status (amputation, inability to ambulate or transfer, needs assistance with daily activities, and being institutionalized), lab values (body mass index (BMI), hemoglobin, serum albumin, and estimated glomerular filtration rate (eGFR)), primary cause of renal failure (hypertension/large vessel disease, diabetes, glomerulonephritis, or other), pre-dialysis nephrology care patterns (no care, 0-6 months, 6-12 months, and >12 months). To maximally capture patient's existing diseases, we used one inpatient or outpatient diagnosis code (either primary or secondary) in the pre-end stage renal disease (ESRD) institutional claims and physician/supplier claims 2 years prior to dialysis to score their comorbid conditions. The major comorbid conditions included were diabetes, hypertension, coronary artery disease (myocardial infarction, atherosclerosis, and coronary revascularization), congestive heart failure, peripheral vascular disease, cerebrovascular disease, dyslipidemia, stroke, chronic obstructive pulmonary disease, cancer, depression, and dementia. Smoking status was also ascertained from the pre-dialysis claims file. ESRD network number, facility profit status and hospital association were

ascertained from the facility file. Days on hemodialysis without an AVF were calculated as time from dialysis initiation to AVF placement.

Statistical Analysis

Derivation and Validation Data sets

We randomly divided the study cohort into two non-overlapping subcohorts-a training data set (9,829, 66%) and a validation data set (5,063, 34%). Baseline patient characteristics and practice patterns were presented, with continuous variables expressed as mean ± SD and categorical variables as frequencies.

Forests Analysis

We used random survival forests (RSF) with competing risks to select predictors for AVF maturation. RSF is an ensemble tree method for the analysis of right censored survival data.[6] Using the training data set, we constructed a RSF based on 1,000 bootstrap samples. Each tree was built from an independent and unique bootstrap sample (**Figure 2)**. Each time when a RSF was build, 1/3 of data were automatically excluded as out-of-bag (OOB) data for validation. At each tree node, we randomly selected a set of variables. The number of variables selected was the square root of the total number of all potential predictors. The variable which had the highest log-rank value was selected to be the best splitting variable. It was used to split the node into two branches. Branches were continued to split until the terminal branches had no fewer than 3 outcomes. The randomness was introduced by both bootstrap sampling of patients from the original cohort and random sampling of variables at each tree node. We also plotted the ensemble cumulative incidence function (CIF) and the cause-specific cumulative hazard function

(CSCHF), which refers to the sum of the hazard function across all the different survival times in the data set. Statistical analyses were performed using SAS (version 9.3; SAS institute, Cary, NC) and package RandomSurvivalForest in R (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria).[7]

Validation of the Prediction Model

Predictive accuracy of the predict model developed from the grown RSF was assessed by the average prediction error calculated both internally using the OOB data and the validation data set. Prediction error is 1 minus Harrell's C statistic (C index). A value of 1 for Harrell's C-statistic corresponds to perfect prediction, while a value of 0.5 indicates prediction does not perform better than random guessing.

Identification of Predictive Variables

The importance of each variable was determined by Brieman-Cutler permutation variable importance, referred as VIMP. VIMP measures change in prediction error average over all trees for a RSF grown with and without a variable. A positive value for VIMP indicates that prediction error increase without the variable and that the variable is predictive. The larger the VIMP, the more predictive the variable is. We used VIMP $\geq$ 0.0005 as a threshold to identify important predictors for AVF maturation by using the average absolute VIMP for noise variables as a reference.[6]

Missing Data Imputation

Preliminary exploration of the data showed missing of serum albumin (26.3%), BMI (0.6%), hemoglobin (8.5%), eGFR (3.2%), facility profit status (0.3%), and facility hospital association (0.3%) at baseline did not follow the pattern of missing completely at random (MCAR). Missing of lab values depended on comorbidity index, BMI, and age at dialysis initiation. It is also possible that the lab values in the normal range were less likely to be reported, so the missing mechanism could be missing not at random (MNAR). We used the RSF embedded method which imputes missing values of the selected variables at the node by random drawings from non-missing in-bag data.[7]

Sensitivity Analyses

We tested the robustness of the prediction ability of these risk factors by two additional analyses. From the first RSF with all 34 potential predictors, we built two subsequent RSFs after removing noise variables with VIMP $\leq$ 0. We checked the consistency of the ranking and relative size of VIMP in these two RSFs. We also repeated our analyses by reconstructing a RSF after excluding observations with missing values. This complete-case analysis allowed us to check whether OOB prediction error and VIMP estimates were biased in RSF built by the imputed data.

RESULTS

Baseline Characteristics

Table 1 presented patient demographics, comorbid conditions, limited functional status, lab values, and quality of care in the study cohort. The mean age of the patient population was 76.7±6.5 years old with 54.5% of male and 76.0% of White. The population carried heavy

disease burdens: 68.7% of them had diabetes, 86.2% were hypertensive, 64.0% had coronary artery disease, and 17.1% needed assistance for daily activities. The mean time from dialysis initiation to AVF placement was 70.8±42.5 days and 45.7% of patients started dialysis without any pre-dialysis nephrology care.

AVF Maturation

Out of 14,892 patients, 50.5% achieved AVF maturation, 12.9% had a competing event, and the remaining 36.6% dialyzed without a useable AVF 6 months after AVF placement (**Table 1**). Among patients whose achieved AVF maturation, the median time to maturation was 4 (IQR: 3-5) months. AVF maturation was more likely to occur in patients who were male, younger than 85 years old, and non-black race. Compared to patients who had a failed AVF or a competing event, they were slightly healthier (diabetes: 66.9% vs. 71.9% or 66.9%; hypertension: 85.6% vs. 86.7% or 87.3%; coronary artery disease: 62.4% vs. 62.9% or 73.5%), had better functional status (need assistance with daily activities: 15.1% vs. 18.1% or 22.4%, being institutionalized: 10.1% vs. 13.1% or 18.7%), and had pre-dialysis nephrology care (no nephrology care: 45.0% vs. 46.3% or 46.4%).

RSF Analysis

A total of 49.7% out of 4,882 patients in the training data set achieved AVF maturation, 13.6% had competing events, and 36.7% remained dialyzing with a CVC within 6 months after AVF placement. The OOB error rate of the RSF was 45.3% for AVF maturation and 40.4% for

competing events, respectively (**Table 2**). From the RSF of 1,000 trees based on 34 variables, gender was the most predictive variable (VIMP, 0.0027), followed by race, being institutionalized, eGFR, BMI, days on dialysis without an AVF, atherosclerosis, and dialysis network by decreasing order of importance (VIMP $\geq$ 0.0005) (**Table 3**). Except gender, all the other variables had smaller VIMP. Variables which did not provide predictive information were: hemoglobin, coronary revascularization, smoke, hypertension, inability to transfer, cerebrovascular disease, and amputation. **Figure 3** showed the ensemble cumulative incidence function (CIF) and cause-specific cumulative hazard function (CSCHF) in the period of 6 months. AVF maturation increased slowly in the first 2 months after placement; however, it accelerated from 2-6 months.

Sensitivity Analyses

After removing 7 variables of which the VIMP $\leq$ 0 including hemoglobin, coronary revascularization, smoke, hypertensions, inability to transfer, cerebrovascular disease and amputation, we built the second RSF with 1,000 bootstrap samples based on 27 potential predictors. Gender, race, being institutionalized, GFR, BMI, and days on dialysis without an AVF remained predictive with VIMP $\geq$ 0.0005 (**Table S1A**). Atherosclerosis and dialysis network, however, were no longer identified as important predictors. The third RSF was built based on 22 variables after further removing 5 variables with VIMP $\leq$ 0 including stroke, age at dialysis initiation, chronic obstructive pulmonary disease, nephrology care, and cancer. It showed the predictors identified with VIMP $\geq$ 0.0005 from the first RSF including gender, race, being institutionalized, GFR, and BMI still had higher VIMP than other predictors (**Table S1B**).

Days on dialysis without an AVF did not appear as a major predictor any more. In both second and third RSF, gender, race, being institutionalized, eGFR, and BMI were qualified as important predictors for AVF maturation above the prerequisite threshold. There was an increasing trend of VIMP with reduced number of predictors, however, the OOB error rate was not significantly improved (from 45.3% to 45.2% and 44.3%, respectively, for the RSFs with 34, 27, and 22 variables) (**Table 2 and Table S2**).

After excluding 4,658 records with missing values, we randomly divided 10,234 observations into a training (6,798) and a testing data set (3,436). A new RSF was built based 34 potential predictors. Among 6,798 patients, 3,411 (50.2%) of them had an AVF matured and 908 (13.4%) had competing events. The OOB error rate was 45.2% for AVF maturation and 41.8% for competing events, respectively. When applied to the validation data set, the OOB error rate was 45.4% for AVF maturation and 58.5% for competing events (**Table S3**). Gender, race, facility profit status, BMI, myocardial infarction, GFR, days on dialysis without an AVF, serum albumin, diabetes, and age at dialysis initiation appeared to have VIMP $\geq$ 0.0005 (**Table S4**).

DISCUSSION

Using a large national cohort of older hemodialysis patients with a newly created AVF, we identify patient's gender as the important predictor for AVF maturation. Race, being institutionalized, eGFR, BMI, and days on hemodialysis without an AVF provide borderline predictive information. However, predictors captured in USRDS data have limited ability to predict AVF maturation.

Gender as an independent risk factor for AVF surgery and maturation has been well documented in previous studies. Allon et al examined factors associated with AVF prevalence in

1,824 patients in the multicenter Hemodialysis (HEMO) Study.[8] They reported gender was the most significant risk factor among all investigated demographic and clinical factors including age, gender, race, BMI, income, education, diabetes, hypertension, coronary artery disease, congestive heart failure, and peripheral vascular disease. Similarly, Peterson et al showed gender was associated with the larger negative effect on AVF maturation as compared to age and AVF location in a group of 205 hemodialysis patients selected by preoperative vascular mapping.[9] In a USRDS study of 9,458 incident hemodialysis patients aged 67 years and older who initiated dialysis between 2010 and 2011, 44% of females received an AVF as compared to 56% of males.[10] Among patients who had an AVF placed, 57% of females had AVF maturation failure and 47% needed one or more interventional procedure to assist maturation as compared to 47% and 40% in males, respectively. The same study also showed gender was associated with higher likelihood of inferior AVF outcomes after maturation. A larger proportion of matured AVF was abandoned in females (21%) than in males (16%). The discrepancy in AVF placement, maturation, assisted maturation, and abandonment persisted after adjusting for age, race, stroke, coronary artery disease, and comorbid score. In addition, our study shows following gender, patient's race and BMI repeatedly present as two predictors with relatively high importance. All three variables might be viewed as proxies for vessel size and configuration.

However, our study indicates that the USRDS data does not include strong variables to predict AVF maturation. This is proved by the very low predictive ability of the models developed by all RSF in this study. Although USRDS routinely collects extensive data on patient clinical and comorbid information, it does not inform on predictors such as arterial and venous vessel size and blood flow from preoperative ultrasound evaluation. As indicated by a recent publication from the Hemodialysis Fistula Maturation (HFM) Study, which was a prospective,

multicenter cohort study examining the association of ultrasound parameters with AVF maturation, three post-operative ultrasound parameters exhibited strong predictive ability for AVF maturation. A prediction model including AVF blood flow, diameter, and depth at 1 day and 2 and 6 weeks after AVF placement achieved C statistics of 0.69, 0.74, and 0.79, respectively for unassisted maturation and 0.69, 0.71, and 0.76, respectively, for overall AVF maturation. Patient's case-mix factors including age, gender, race, dialysis status, diabetes, BMI and AVF location (forearm versus upper arm) were not associated with unassisted or overall AVF maturation.[11] We highly recommend future studies further evaluate these parameters for possibilities to include ultrasound evaluation as a routine clinical practice.

There are several advantages to using RSF. As an extension of random forests, RSF is a highly used machine learning method that gradually gained much popularity in the field of epidemiology.[12,13] Different from traditional statistical methods such as Cox proportional hazards model which has to reply on proportional hazards assumption, RSF does not depend on any distribution assumption and can accommodate non-linear effects or higher order interactions for predictors.

Certain weakness in this study should be noted. First and foremost, the USRDS data does not contain strong predictors which can be linked to biological processes of maturation. When a covariate for maturation is absent in the data, RSF can miss it as an important predictor. Secondly, our study only includes older patients (≥ 67 years), and may not generalize to younger dialysis patients. Thirdly, we are unable to validate the model developed in an external population of patients.

CONCLUSION

In conclusion, the USRDS data may not include the strong predictors and has limited ability to predict AVF maturation. Among the available predictors, patient's gender might be considered as the most important predictor for AVF maturation.

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Table 1. Baseline characteristics of older patients who initiated hemodialysis with a catheter and had subsequent arteriovenous fistula (AVF) placement.

	Total	AVF matured	No event	Died/TX/PD
Total cohort	**14,892**	**7,518(50.5)**	**5,453(36.6)**	**1,921(12.9)**
Demographics				
Age at dialysis initiation (yrs)(mean±SD)	76.7±6.5	76.6±6.4	76.5±6.4	77.7±6.7
67-<75	6,196(41.6)	3,155(42.0)	2,344(43.0)	697(36.3)
75-<85	6,641(44.6)	3,367(44.8)	2,393(43.9)	881(45.9)
≥85	2,055(13.8)	996(13.3)	716(13.1)	343(17.9)
Gender				
Male	8,115(54.5)	4,515(60.1)	2,508(46.0)	1,092(56.9)
Female	6,777(45.5)	3,003(39.9)	2,945(54.0)	829(43.2)
Race				
White	11,322(76.0)	5,788(77.0)	3,910(71.7)	1,624(84.5)
Black	2,755(18.5)	1,270(16.9)	1,243(22.8)	242(12.6)
Other/unknown	815(5.5)	460(6.1)	3,00(5.5)	55(2.9)
Comorbid conditions				
Primary cause of renal failure				
Hypertension/Large vessel disease	5,453(36.6)	2,756(36.7)	1,955(35.9)	742(38.6)
Diabetes	6,236(41.9)	3,090(41.1)	2,445(44.8)	701(36.5)
Glomerulonephritis	527(3.5)	309(4.1)	161(3.0)	57(3.0)
Other	2,676(18.0)	1,363(18.1)	892(16.4)	421(21.9)
Diabetes	10,235(68.7)	5,028(66.9)	3,921(71.9)	1,286(66.9)
Hypertension	12,839(86.2)	6,433(85.6)	4,730(86.7)	1,676(87.3)
Coronary artery disease	9,533(64.0)	4,694(62.4)	3,428(62.9)	1,411(73.5)
Myocardial infarction	3,665(24.6)	1,719(22.9)	1,319(24.2)	627(32.6)
Atherosclerosis	9,227(62.0)	4,543(60.4)	3,312(60.7)	1,372(71.4)
Coronary revascularization	854(5.7)	424(5.6)	299(5.5)	131(6.8)
Congestive heart failure	10,463(70.3)	5,094(67.8)	3,839(70.4)	1,530(79.7)
Peripheral vascular disease	7,848(52.7)	3,830(50.9)	2,871(52.7)	1,147(59.7)
Cerebrovascular disease	4,670(31.4)	2,294(30.5)	1,747(32.0)	629(32.7)
Dyslipidemia	10,823(72.7)	5,455(72.6)	3,957(72.6)	1,411(73.5)
Stroke	1,785(12.0)	827(11.0)	696(12.8)	262(13.6)
Chronic obstructive pulmonary disease	5,757(38.7)	2,750(36.6)	2,081(38.2)	926(48.2)
Cancer	2,968(19.9)	1,517(20.2)	1,011(18.5)	440(22.9)
Depression	2,437(16.4)	1,135(15.1)	956(17.5)	346(18.0)
Dementia	995(6.7)	462(6.2)	387(7.1)	146(7.6)
Smoke	1,431(9.6)	725(9.6)	518(9.5)	188(9.8)
Limited functional status				
Amputation	191(1.3)	98(1.3)	61(1.1)	32(1.7)
Inability to ambulate	1,239(8.3)	499(6.6)	499(9.2)	241(12.6)
Inability to transfer	616(4.1)	238(3.2)	257(4.7)	121(6.3)
Needs assistance with daily activities	2,552(17.1)	1,133(15.1)	988(18.1)	431(22.4)
Being institutionalized	1,835(12.3)	759(10.1)	716(13.1)	360(18.7)
Lab values				
Body mass index (kg/m^2)(mean±SD)	28.5±7.3	28.2±7.0	28.9±7.5	28.1±7.4
Hemoglobin (g/dl, mean ± SD)	10±13.6	10.2±18.9	9.8±2.4	10±3.3
Serum albumin (g/dl, mean ± SD)	3.2±5.5	3.3±6.4	3.1±0.8	3.4±8.4
GFR (ml/min/1.73 m^2, mean ± SD)	13.1±5.6	12.8±5.5	13.1±5.6	14.3±5.8
Care patterns				
Duration of CVC dependency (days, mean ± SD)	70.8±42.5	69.7±41.7	72.7±43.7	69.8±42
Nephrology care				
No care	6,799(45.7)	3,383(45.0)	2,525(46.3)	891(46.4)

0-6 months	2,311(15.5)	1,184(15.8)	815(15.0)	312(16.2)
6-12 months	2,393(16.1)	1,231(16.4)	854(15.7)	308(16.0)
12 months	3,389(22.8)	1,720(22.9)	1,259(23.1)	410(21.3)
Facility type				
Hospital-based	1,320(8.9)	733(9.8)	445(8.2)	142(7.4)
Freestanding	13,532(91.1)	6767(90.2)	4,991(91.8)	1,774(92.6)
Profit status				
For-profit	12,460(83.9)	6,153(82.0)	4,653(85.6)	1,654(86.3)
Non-profit	2,316(15.6)	1,310(17.5)	749(13.8)	257(13.4)
Unknown	76(0.5)	37(0.5)	34(0.6)	5(0.3)

GFR: Glomerular filtration rate. Missing values: BMI 0.6%; hemoglobin 8.5%; albumin 26.3%; GFR 3.2%.

Table 2. Summary output from Random Survival Forests (RSF) analysis based on 34 potential predictors in training and testing data sets.

	Training	Testing
Sample size	9,829	5,063
Number of events	4,882 and 1,340	2,636 and 581
Number of trees	1,000	1,000
Number of variables tried at each split	6	6
Total number of variables	34	34
OOB error rate for AVF maturation	45.3%	45.8%
OOB error rate for competing events	40.4%	39.3%

Table 3. Variable importance (VIMP) of 34 potential predictors for arteriovenous fistula (AVF) maturation and competing events from Random Survival Forests (RSF) analysis of 1,000 trees with 6 variables at each split.

	VIMP	
Potential predictors	**AVF maturation**	**Competing events**
Gender	0.0027	-0.0003
Race	0.0008	0.0028
Being institutionalized	0.0007	0.0026
Estimated glomerular filtration rate	0.0007	0.0028
Body mass index	0.0007	0.0009
Days on dialysis without an AVF	0.0007	0.0003
Atherosclerosis	0.0006	0.0007
Network	0.0005	0.0016
Congestive heart failure	0.0004	0.0013
Facility profit status	0.0004	0.0001
Myocardial infarction	0.0004	0.0024
Region	0.0004	0.0015
Age at dialysis initiation	0.0003	0.0014
Needs assistance with daily activities	0.0003	0.0003
Primary cause of renal failure	0.0003	0.0009
Peripheral vascular disease	0.0003	0.0001
Cancer	0.0003	0.0003
Depression	0.0003	0.0000
Diabetes	0.0002	0.0002
Serum albumin	0.0002	-0.0002
Facility hospital association	0.0002	0.0000
Nephrology care	0.0002	0.0001
Dementia	0.0001	0.0001
Chronic obstructive pulmonary disease	0.0001	0.0012
Dyslipidemia	0.0001	-0.0003
Inability to ambulate	0.0001	0.0004
Stroke	0.0001	0.0002
Amputation	0.0000	0.0000
Cerebrovascular disease	0.0000	0.0003
Inability to transfer	0.0000	0.0002
Hypertension	0.0000	-0.0001
Smoke	-0.0001	-0.0001
Coronary revascularization	-0.0001	0.0001
Hemoglobin	-0.0002	0.0007

Figure 1. Development of the study cohort.

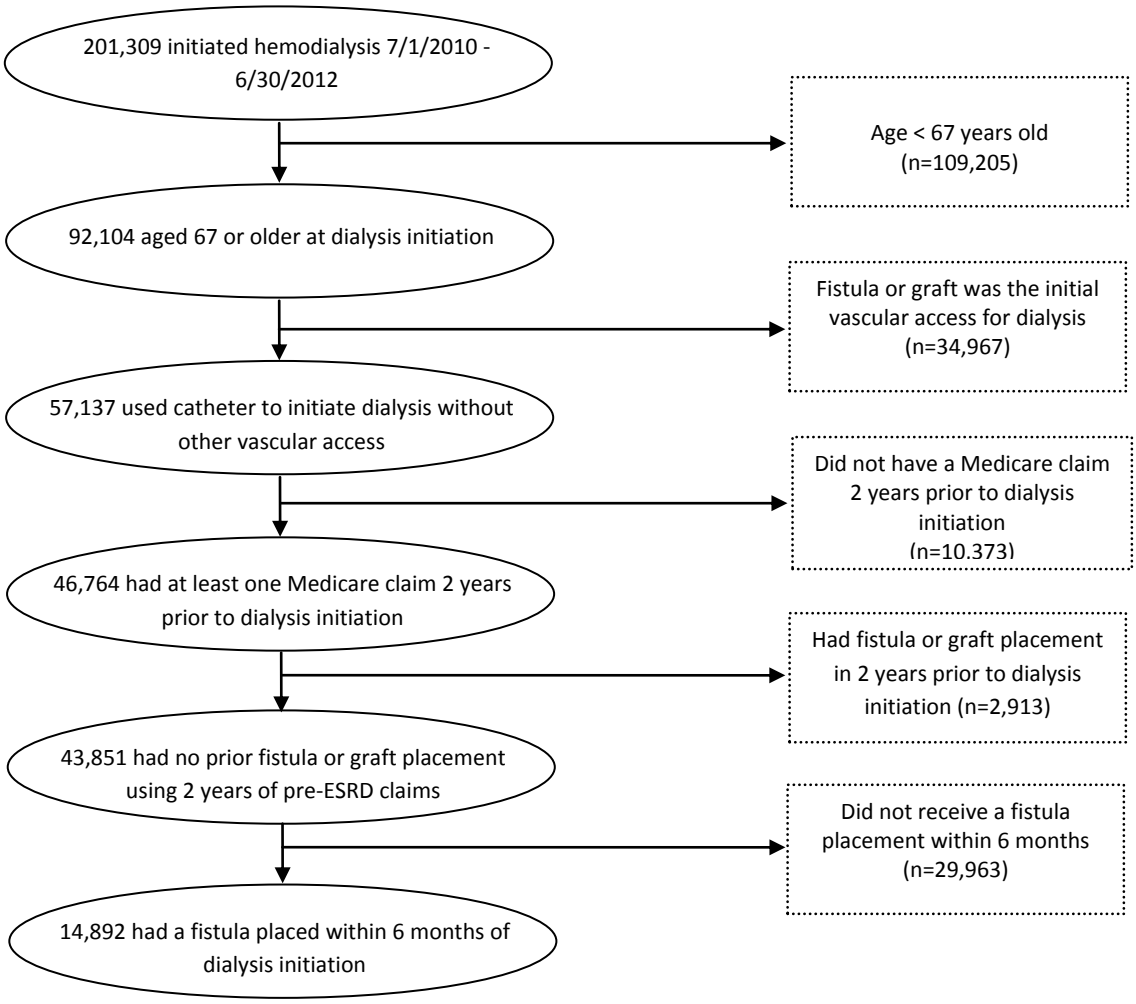

201,309 initiated hemodialysis 7/1/2010 - 6/30/2012
Age < 67 years old (n=109,205)
92,104 aged 67 or older at dialysis initiation
Fistula or graft was the initial vascular access for dialysis (n=34,967)
57,137 used catheter to initiate dialysis without other vascular access
Did not have a Medicare claim 2 years prior to dialysis initiation (n=10.373)
46,764 had at least one Medicare claim 2 years prior to dialysis initiation
Had fistula or graft placement in 2 years prior to dialysis initiation (n=2,913)
43,851 had no prior fistula or graft placement using 2 years of pre-ESRD claims
Did not receive a fistula placement within 6 months (n=29,963)
14,892 had a fistula placed within 6 months of dialysis initiation

Figure 2. Example of a random tree. A bootstrap sample of patients from the original data set is used to create a random tree. At the root, a random set of variables is selected to be candidates, and the most predictive variable for survival among those is identified. Node levels are numbered based on their relative distance to the trunk of the tree. Splitting of nodes to create the tree continues until terminal nodes have few distinct outcomes.

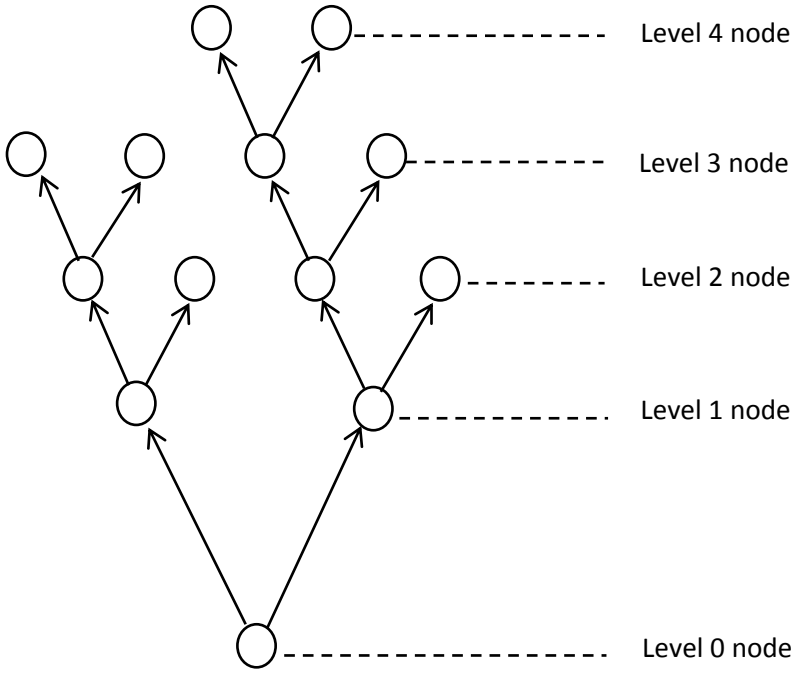
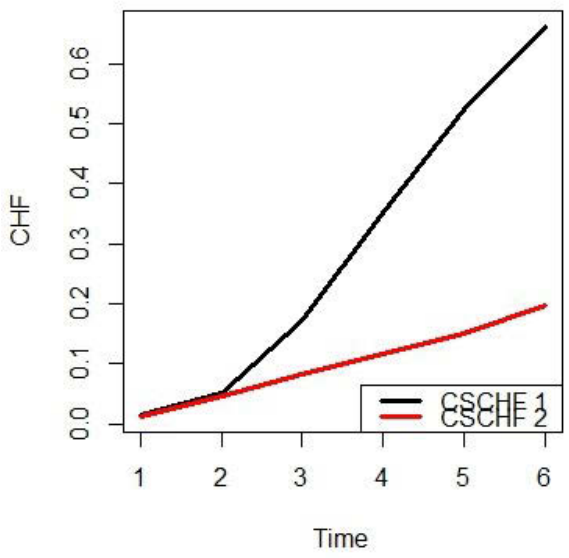

Level 4 node
Level 3 node
Level 2 node
Level 1 node
Level 0 node
Bootstrap sample

Figure 3. The cause-specific cumulative hazard function (CSCHF) and ensemble cumulative incidence function (CIF) for arteriovenous fistula (AVF) maturation (black line) and competing events (red line) from a competing risk analysis in hemodialysis patients aged 67 and older. The unit of time is month. Competing events: death, kidney transplant, or peritoneal dialysis transfer.


CHF
0.0
0.1
0.2
0.3
0.4
0.5
0.6
1
2
3
4
5
6
Time
CSCHF 1
CSCHF 2

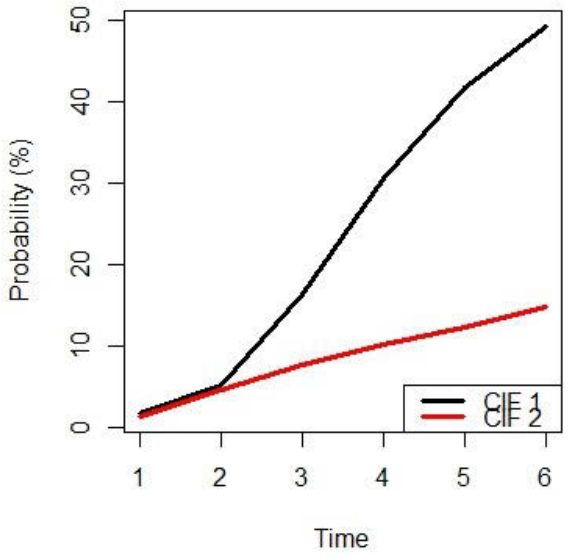

Probability (%)
0
10
20
30
40
50
1
2
3
4
5
6
Time
CIF 1
CIF 2

Table S1A. Variable importance (VIMP) of 27 potential predictors for arteriovenous fistula (AVF) maturation and competing events from Random Survival Forests (RSF) analysis of 1,000 trees with 6 variables at each split.

	VIMP	
Potential predictors	**AVF maturation**	**Competing events**
Gender	0.0029	0.0000
Race	0.0009	0.0027
Days on dialysis without an AVF	0.0007	0.0008
Glomerular filtration rate	0.0006	0.0029
Body mass index	0.0006	0.0007
Being institutionalized	0.0006	0.0025
Myocardial infarction	0.0005	0.0026
Facility profit status	0.0005	-0.0001
Peripheral vascular disease	0.0004	0.0002
Region	0.0003	0.0016
Congestive heart failure	0.0003	0.0010
Diabetes	0.0003	0.0003
Network	0.0003	0.0012
Inability to ambulate	0.0003	0.0006
Dyslipidemia	0.0002	-0.0002
Atherosclerosis	0.0002	0.0007
Dementia	0.0002	0.0001
Depression	0.0002	-0.0001
Facility hospital association	0.0001	0.0000
Serum albumin	0.0001	-0.0001
Primary cause of renal failure	0.0001	0.0008
Needs assistance with daily activities	0.0001	0.0005
Cancer	0.0000	0.0005
Nephrology care	0.0000	0.0000
Chronic obstructive pulmonary disease	0.0000	0.0014
Age at dialysis initiation	0.0000	0.0016
Stroke	-0.0001	0.0001

Table S1B. Variable importance (VIMP) of 22 potential predictors for arteriovenous fistula (AVF) maturation and competing events from Random Survival Forests (RSF) analysis of 1,000 trees with 6 variables at each split.

	VIMP	
Potential predictors	**AVF maturation**	**Competing events**
Gender	0.0040	-0.0002
Race	0.0016	0.0039
Body mass index	0.0012	0.0010
Region	0.0012	0.0021
Being institutionalized	0.0011	0.0032
Glomerular filtration rate	0.0011	0.0029
Network	0.0010	0.0017
Primary cause of renal failure	0.0009	0.0008
Days on dialysis without an AVF	0.0009	0.0018
Congestive heart failure	0.0008	0.0015
Facility profit status	0.0007	0.0000
Myocardial infarction	0.0007	0.0033
Diabetes	0.0007	0.0006
Atherosclerosis	0.0006	0.0009
Dyslipidemia	0.0004	-0.0006
Inability to ambulate	0.0004	0.0007
Needs assistance with daily activities	0.0003	0.0004
Serum albumin	0.0003	-0.0002
Facility hospital association	0.0003	0.0001
Depression	0.0003	0.0002
Dementia	0.0002	0.0000
Peripheral vascular disease	0.0001	0.0004

T**able S2.** Summary output from Random Survival Forests (RSF) analysis based on 27 and 22 variables in training data set.

Total number of variables	27	22
Sample size	9,829	9,829
Number of events	4,882 and 1,340	4,882 and 1,340
Number of trees	1,000	1,000
Number of variables tried at each split	6	6
OOB error rate for AVF maturation	45.2%	44.3%
OOB error rate for competing events	40.5%	41.1%

Table S3. Summary output from Random Survival Forests (RSF) analysis based on 34 potential predictors in training and validation data sets without imputation

.

	Training	Validation
Sample size	6,798	3,436
Number of events	3,411 and 908	1,806 and 386
Number of trees	1,000	1,000
Number of variables tried at each split	6	6
Total number of variables	34	34
OOB error rate for AVF maturation	45.2%	45.4%
OOB error rate for competing events	41.8%	38.5%

Table S4. Variable importance (VIMP) of 34 potential predictors for arteriovenous fistula (AVF) maturation and competing events from Random Survival Forests (RSF) analysis of 1,000 trees with 6 variables at each split without imputation.

	VIMP	
Potential predictors	**AVF maturation**	**Competing events**
Gender	0.0022	-0.0001
Race	0.0009	0.0037
Facility profit status	0.0008	0.0000
Body mass index	0.0008	0.0001
Myocardial infarction	0.0006	0.0016
Glomerular filtration rate	0.0006	0.0017
Days on dialysis without an AVF	0.0006	0.0003
Serum albumin	0.0005	-0.0003
Diabetes	0.0005	0.0002
Age at dialysis initiation	0.0005	0.0010
Region	0.0004	0.0009
Being institutionalized	0.0003	0.0025
Congestive heart failure	0.0002	0.0011
Facility hospital association	0.0002	-0.0001
Network	0.0002	0.0006
Inability to ambulate	0.0002	0.0012
Dyslipidemia	0.0001	-0.0006
Needs assistance with daily activities	0.0001	0.0001
Cerebrovascular disease	0.0001	0.0000
Amputation	0.0001	0.0000
Dementia	0.0001	-0.0001
Chronic obstructive pulmonary disease	0.0000	0.0006
Inability to transfer	0.0000	0.0001
Depression	0.0000	0.0002
Cancer	0.0000	0.0006
Stroke	0.0000	0.0000
Peripheral vascular disease	0.0000	-0.0004
Hypertension	0.0000	0.0000
Smoke	0.0000	0.0002
Coronary revascularization	0.0000	-0.0001
Primary cause of renal failure	-0.0001	0.0006
Atherosclerosis	-0.0001	0.0002
Nephrology care	-0.0001	0.0003
Hemoglobin	-0.0002	0.0004

CHAPTER SIX

CLINICAL MEDICINE AND PUBLIC HEALTH IMPLICATIONS FOR VASCULAR ACCESS USE IN OLDER HEMODIALYSIS PATIENTS

PART ONE: INDIVIDUALIZED VASCULAR ACCESS STRATEGY

"Fistula First" or "Graft First" Based on Age

Arteriovenous Fistula Interventions and Revisions

Arteriovenous Fistula Maturation Prediction

PART TWO: PRACTICE PATTERNS IMPROVEMENT

Arteriovenous Fistula Early Placement

Disparities in Arteriovenous Fistula Care

PART THREE: SUMMERY

Clinical Medicine Implications

Public Health Implications

The principle findings of our studies in older hemodialysis patients could be summarized as: (1) only a small proportion of patients have completed the sequential stages from initial AVF placement to achieving the goal of AVF patency; and (2) increasing age is significantly associated with lower probability of AVF placement and maturation. Although our studies indicated the chance of AVF maturation should be the most important consideration for vascular access planning, we are not able to establish a clinically friendly model to predict AVF maturation for older patients on dialysis. Results of our studies have important implications for vascular access selection and development in older hemodialysis patients.

PART ONE: INDIVIDUALIZED VASCULAR ACCESS STRATEGY

As arteriovenous fistula (AVF) continues to be the favorable vascular access for most of hemodialysis patients, there is an increasing call for individualized vascular access strategies for dialysis patients.[1-3] The new 2018 KDOQI Vascular Access Practice Guidelines moves away from the "Fistula First" strategy and emphasizes a more patient-centered approach.[4]

"Fistula First" or "Graft First" Based on Age

Our study demonstrates "Fistula First" is not the best vascular access strategy for every older adult undergoing hemodialysis. The proper candidates should be those who have a strong possibility of achieving a matured AVF. More importantly, they should have a reasonable life expectancy to reap the post-maturation benefits of an AVF. Thus, "Fistula First" strategy may not be superior to "Graft First" in very old hemodialysis patients, e.g. octogenarians and nonagenarians. Firstly, as shown by our study, increasing age is significantly associated with decreased chance of AVF maturation. Secondly, when placing an AVF in a very old hemodialysis patient with a limited life expectancy, we need to justify the short-time benefits brought by AVF against the potential harm caused by CVC use while waiting. Nationally, the average life expectancy for patients on dialysis aged 80 to 84, and 85 years and older were 2.7 and 2.2 years, respectively.[5] Our study shows the median waiting time for AVF maturation is approximately 5 months. AVF use for a short period of time may not worth the risk of dialyzing with a CVC to get an AVF matured. Nevertheless, arteriovenous graft (AVG) takes much less time and efforts to reach successful use (~ 2 to 4 weeks) as compared to AVF. For patients with short life expectancy and high probability of AVF failure, AVG may be a better choice. On the

other hand, our study supports placing AVF as the initial vascular access in patients 67 to 76 years old. The likelihood of AVF maturation is similar in patients from 67 to 76 years old and higher than those aged 77 and older. Placing AVF in patients of this population may bring long-term benefits since older adults aged 70 to 74 and 75-79 on hemodialysis may expect to live up to 3.8 and 3.3 years on average.[5] If life expectancy estimated based on an individual's frailty, clinical situation, and comorbid condition is more than 2 years, AVF placement, especially for those with a great chance of AVF maturation, might bring overall benefits.

Fistula Interventions and Revisions

Our study demonstrates a substantial portion of AVF maturation was facilitated by endovascular or surgical interventions and AVF patency was maintained by frequent revisions. Again, these procedures could be brought as one of the consequences of improper selection of AVF candidates encouraged by financial incentives provided by "Fistula First". Requirement for these procedures frequently prolongs CVC dependence. In addition, patient quality of life suffers from repeated procedures, which are time-consuming, painful and disruptive to their dialysis therapy. These procedures also translate into greater costs for vascular access management. The clinician must consider the option of AVG placement in some patients, who have poor venous or arterial anatomy, to minimize the need for assisted AVF interventions.

Fistula Maturation Prediction

There is an urgent need of knowledge to identify patients with a higher chance of AVF maturation. However, our study shows the decrease in predicted accuracy of Lok's risk equation

for primary failure is of such a degree that the model appears useless for clinical decision-making of vascular access choice in older dialysis patients. In addition, variables captured in the USRDS data have limited ability to predict AVF maturation. As indicated by a recent publication from the Hemodialysis Fistula Maturation (HFM) Study, which is a prospective, multicenter cohort study examining the association of ultrasound parameters with AVF maturation, three post-operative ultrasound parameters exhibit strong predictive ability for AVF maturation. A prediction model including AVF blood flow, diameter, and depth achieved good discriminative accuracy for unassisted maturation and overall AVF maturation.[6] When these ultrasound parameters are included in the prediction model, patient's case-mix factors (age, gender, race, dialysis status, diabetes, BMI and AVF location) are not associated with unassisted or overall AVF maturation. This study indicates ultrasound parameters after AVF placement have great potential to predict AVF maturation. We highly recommend future studies further evaluate these parameters for possibilities to include ultrasound evaluation as a routine clinical practice.

PART TWO: PRACTICE PATTERNS IMPROVEMENT

Early Placement of Arteriovenous Fistula

To effectively decrease CVC use, future efforts could be directed at minimizing time between the start of dialysis and AVF placement or having AVF placed before dialysis. Our study shows, nationally, the median time for AVF placement among older patients who initiated dialysis with a CVC is 2 months after dialysis initiation. This is far from reaching the standard of

placing an AVF 6 months prior to dialysis proposed by the 2006 and 2018 KDOQI clinical guidelines. [4,7] If AVFs could be placed early, more time are available for AVF to develop, be intervened, and mature so that central venous catheter (CVC) use is avoided.

However, current reimbursement policy does not have any financial incentives to promote predialysis care and there is inadequate reimbursement to encourage surgeons for AVF placement.[8] Timely placement of AVF needs both system and provider level efforts, for example, having a defined care pathway that includes patient education, higher eGFR thresholds for surgical referral and AVF placement, and a patient tracking database.

Disparities in Fistula Care

Although "Fistula First" has been publicized for more than 15 years, our study demonstrates moderate geographic disparities in vascular access care. Especially, the rates of AVF placement and patency loss are not uniformly distributed throughout the country. This reflects difference in patterns of practice in dialysis facilities. Even under the same "Fistula First" policy, some facilities are highly motivated to construct AVFs, while others leave more patients dialyzing with a CVC. Some facilities revise AVFs more frequently than others to maintain dialysis delivery. Some discard AVFs more frequently than others and replace them with new vascular access. We suggest that attention should be especially paid to facilities who had low AVF placement rate and yet high rates of primary and secondary patency loss. In these facilities, patients wait longer to get an AVF placed. Higher rates of patency loss also indicate improper candidates for AVFs, i.e., those with "borderline" vascular features, were selected for AVF placement. Addressing these disparities will improve AVF-related vascular access outcomes.

PART THREE: SUMMARY

Clinical Medicine Implications

In summary, we recommend clinical practice uses the combination of the estimated probability of AVF maturation and life expectancy as the standard to select candidates for AVF placement in older hemodialysis patients. For octogenarians and nonagenarians, AVG should be placed as the primary vascular access to avoid prolonged CVC use at the beginning of dialysis. We also recommend exploring the feasibility of using ultrasound evaluation as a routine clinical practice to predict AVF maturation in future studies. Accurately predicting the likelihood of AVF maturation will help reduce the medical and economical burdens of AVF interventions and revisions.

Public Health Implications

We suggest Centers for Medicare and Medicaid Services (CMS) adjusts current financial policy to encourage early AVF placement in proper candidates or even consider extend financial coverage for pre-dialysis vascular access care among older hemodialysis patients so CVC use could be reduced or avoided. In addition, they may consider incorporating AVF/AVG patency as one of the care index into clinical performance measures (CPM) to establish a comprehensive system to evaluate vascular access outcomes.

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APPENDIX

PART I. Sample SAS Codes for Restricted Cubic Splines (RCS)

```
ods graphics on;
ods rtf file='rcs_place.rtf;
%include "/jzhang/sas/careaim1/cohort1/RCS_Regplace.sas";
%RCS_Reg(infile=cohort,main_spline_var=inc_age,
no_title=1,no_label_x=0,no_label_y=0,no_legend=1,display_knots=0,avk_msv=0,x_ref_line=0,
y_ref_line=1,
typ_reg=cox,dep_var=status_placenew1,surv_time_var=time_place);
ods rtf close;
ods graphics off;
```

PART II. Sample SAS Codes for Subdistribution Proportional Hazards Regression

```
*Subdistribution hazard ratio (SHR) for AVF placement;
*Age as 2 categories;
proc phreg data=my.cohort1c1;
      class age_2cat/descending;
      model time_place*status_place1(0)=age_2cat/eventcode=1 rl;
run;

proc phreg data=my.cohort1c1;
      class age_2cat sex_cat race_cat diabetes hyper stroke mi revas chf cva cancer func nephnew
region/descending;
      model time_place*status_place1(0)=age_2cat sex_cat race_cat diabetes hyper stroke mi
revas chf cva cancer func nephnew region cci bmi album gfr_mdrd/eventcode=1 rl;
run;

*Subdistribution hazard ratio (SHR) for death;
proc phreg data=my.cohort1c1;
      class age_2cat/descending;
      model time_place*status_place1(0)=age_2cat/eventcode=2 rl;
run;

proc phreg data=my.cohort1c1;
          class age_2cat sex_cat race_cat diabetes hyper stroke mi revas chf cva cancer func
nephnew region/descending;
      model time_place*status_place1(0)=age_2cat sex_cat race_cat diabetes hyper stroke mi
revas chf cva cancer func nephnew region cci bmi album gfr_mdrd/eventcode=2 rl;

run;
```

PART III. Sample SAS Codes for Crude and Inverse Probability Weighted Cumulative Incidence Function (CIF)

```
*Set graph options;
goptions device=png targetdevice=png gsfname=grafout gsfmode=replace xpixels=1500
ypixels=1200;
axis1 label=(height=2 "Days") value=(font="Times" height=2) order=(0 365 730 1095);
axis2 label=(angle=90 height=2 "AVF Placement (Bottom)") order=(0.0 0.2 0.4 0.6 0.8 1.0)
value=(font="Times" height=2);
axis3 label=(angle=90 height=2 "Competing Events (Top)") order=(1.0 0.8 0.6 0.4 0.2 0.0)
value=(font="Times" height=2);

legend1 across=1 position=(bottom right inside) noframe label=none shape=line(5)
value=(justify=left font="Times"
height=2.5 "67-<77" "77+");
symbol1 c=black l=1 w=3 v=none i=stepjs;
symbol2 c=black l=3 w=3 v=none i=stepjs;
symbol3 c=black l=1 w=3 v=none i=stepjs;
symbol4 c=black l=3 w=3 v=none i=stepjs;

ods rtf file='CIF AVF placement crude.rtf';
proc gplot data=cif_cd;
      plot cif1*time_place=age_2cat/nolegend haxis=axis1 vaxis=axis2;
         plot2 cif2*time_place=age_2cat/vaxis=axis3 legend=legend1;
      title1 font="Times" height=2.5 "Crude Cumulative Incidence Function (CIF)";
run;

ods rtf close;


*Weighted CIFs;
*Calculate weights;
proc logistic descending data=my.cohort1c1 noprint;
      model age_2cat=;
      output out=o1 prob=tn;
run;
proc logistic descending data=my.cohort1c1 noprint;
         class sex_cat race_cat diabetes hyper stroke mi revas chf cva cancer func nephnew
region;
      model age_2cat=sex_cat race_cat diabetes hyper stroke mi revas chf cva cancer func
nephnew region cci bmi album gfr_mdrd;
      output out=o2 prob=td;
run;
proc sort data=o1;by usrds_id;run;
proc sort data=o2;by usrds_id;run;
data o12;
```

```
	merge o1 o2;
	by usrds_id;
run;
data b(drop=_level_ tn td);
	set o12;
	by usrds_id;
	if age_2cat='0' then do;tn=1-tn;td=1-td;end;
	tw=1/td;
	stw=tn/td;
run;

*Weighted CIF in competing risk analysis;
proc lifetest data=b outcif=cif3;
	time time_place*status_place1(0)/eventcode=1;
	freq stw/notruncate;
	   strata age_2cat;
run;

proc lifetest data=b outcif=cif4;
	time time_place*status_place1(0)/eventcode=2;
	freq stw/notruncate;
	   strata age_2cat;
run;

proc sort data=cif3;by age_2cat time_place;run;
proc sort data=cif4;by age_2cat time_place;run;

data cif_wt;
	merge cif3(in=x rename=(cif=cif3)) cif4(in=y rename=(cif=cif4));
	by age_2cat time_place;
	if x and y;
run;

*Set graph options;
goptions device=png targetdevice=png gsfname=grafout gsfmode=replace xpixels=1500
ypixels=1200;
axis1 label=(height=2 "Days") value=(font="Times" height=2) order=(0 365 730 1095);
axis2 label=(angle=90 height=2 "AVF Placement (Bottom)") order=(0.0 0.2 0.4 0.6 0.8 1.0)
value=(font="Times" height=2);
axis3 label=(angle=90 height=2 "Competing Events (Top)") order=(1.0 0.8 0.6 0.4 0.2 0.0)
value=(font="Times" height=2);

legend1 across=1 position=(bottom right inside) noframe label=none shape=line(5)
value=(justify=left font="Times"
height=2.5 "67-<77" "77+");
symbol1 c=black l=1 w=3 v=none i=stepjs;
```

```
symbol2 c=black l=3 w=3 v=none i=stepjs;
symbol3 c=black l=1 w=3 v=none i=stepjs;
symbol4 c=black l=3 w=3 v=none i=stepjs;


ods rtf file='CIF AVF placement weighted.rtf';
proc gplot data=cif_wt;
      plot cif3*time_place=age_2cat/nolegend haxis=axis1 vaxis=axis2;
      plot2 cif4*time_place=age_2cat/vaxis=axis3 legend=legend1;
      title1 font="Times" height=2.5 "Weighted Cumulative Incidence Function (CIF)";
run;
ods rtf close;
```

PART IV. Sample SAS Codes for Testing Proportional Hazards Assumption;

```
%let GraphOpts=attrpriority=none DataContrastColors=(black) DataColors=(black);

ods rtf file='proportional check_place.rtf';

*Cause-specific;
*Log of negative log of survival vs. log of time;
proc lifetest data=my.cohort1c1 plot(only)=(lls) noprint;
      time time_place*status_place1(0,2);
      strata age_2cat;
         label time_place='Months';
run;
ods rtf close;

*time-age interaction;
proc phreg data=my.cohort1c1;
      class age_2cat/descending;
      model time_place*status_place1(0,2)=age_2cat time_age/rl;
time_age=time_place*age_2cat;
run;

*Subdistribution;
*time-age interaction;
proc phreg data=my.cohort1c1;
      class age_2cat/descending;
      model time_place*status_place1(0)=age_2cat time_age/eventcode=1 rl;
time_age=time_place*age_2cat;
run;
```

PART V. SAS Codes for C Statistics;

```
ods graphics on;
ods rtf file='Figure 2.C statistics_black&white.rtf' style=journal;
proc logistic data=my.cohortnew2;
	model status_failure(event="1")=;
	roc pred=prob_failure;
roccontrast;
run;
ods rtf close;
ods graphics off;
```

PART VI. SAS Codes for Calibration Plot;

```
ods graphics on;
ods rtf file='Figure 3. Calibration plot_black&white.rtf' style=journal;
proc sgplot data=cali noautolegend aspect=1;
	lineparm x=0 y=0 slope=1/lineattrs=(color=gray pattern=dash);
	loess x=prob_failure y=prob_obs;
	scatter x=prob_failure y=prob_obs;
	yaxis label='Observed Probability of Fistula Failure' values=(0 to 0.7 by 0.1);
	xaxis label='Predicted Probability of Fistula Failure' values=(0 to 0.7 by 0.1);

run;
ods rtf close;
```

PART VII. SAS Codes for Training and Validation Data Sets

```
*randomly divide the cohort to training (2/3) and validation (1/3) subcohorts;
proc surveyselect data=cohort samprate=0.66 seed=12345 out=cohort_select outall
      method=srs noprint;
run;

*check;
proc freq data=cohort_select;tables selected/list;run;
data one (drop=selected) two(drop=selected);
          set cohort_select;
          if selected=1 then output one;
          else if selected=0 then output two;
run;
```

PART VIII. Sample R Codes for Random Survival Forests with Competing Risks

```
##Install package
install.packages("randomForestSRC")

##Set pathway
setwd("C:/Users/ Desktop/prediction")

##Load package in memory
library(randomForestSRC)


##Read CSV into R
rsftrain<-read.csv(file="rsftrain.csv",header=TRUE,sep=",")

##Define factors
##Censoring variable must be numeric
rsftrain$sex_cat<-factor(rsftrain$sex_cat)
rsftrain$race_cat<-factor(rsftrain$race_cat)
….

##Build a forest
##bootstrap is default, by.root
##importance is default, importance=TRUE, computationally expensive
##cause=2, two event of interest
set.seed(123)
rsf.grow<-
rfsrc(Surv(time_mature,status_mature)~.,cause=2,importance=c("TRUE"),data=rsftrain,ntree=10
00,na.action="na.impute")

##Save the forest
saveRDS(rsf.grow,file="rsf.RDS")
rsf.grow<-readRDS("rsf.RDS")

##Error rate
print(rsf.grow)

##Variable importance (VIMP)
plot(rsf.grow,plots.one.page=FALSE,sorted=TRUE,verbose=TRUE)

##Minimal depth
var.select(object=rsf.grow,method="md",conservative="high")

#Plot CIF and CSCHF
plot.competing.risk(rsf.grow,plots.one.page=TRUE)
```

```
##Predict in the test data
rsftest<-read.csv(file="rsftest.csv",header=TRUE,sep=",")
summary(rsftest)

##Test the forest
rsf.predict<-
predict(rsf.grow,newdata=rsftest,outcome="test",na.action="na.impute",importance=c("TRUE"))

#Print error rate in the testing dataset
print(rsf.predict)
```

BIOGRAPHICAL STATEMENT

Joyce Qian was born in Fushun, Liaoning Province, China. She received a bachelor's degree in Marine Biology from Xiamen University and a master's degree in Marine Science from College of William and Mary. She was introduced to the classic textbook "Epidemiology in Medicine" during her work, which fostered her desire for a career change and pursuit of an advanced degree in epidemiology. After she obtained a master degree of public health in epidemiology from Virginia Commonwealth University, she worked as an agency management specialist at Division of Disease Prevention, Virginia Department of Health, and a staff research associate at San Francisco Veterans Affairs Medical Center. Currently, she is an epidemiologist at Medical Technology and Practice Patterns Institute (MTPPI) at Bethesda, Maryland, where she provides advanced study design and analytical support for grant applications on health services and kidney diseases research. In 2015, she enrolled in Bloomberg as a Ph.D. student in the track of General Epidemiology and Methodology. At Bloomberg, she received the Ellen B. Gold Fund for Epidemiology Scholarship and worked as a teaching assistant for Epidemiologic Methods 752 and 753. Joyce has published 12 papers and has another 3 under review. She lives in Potomac, Maryland with her husband and their daughter.